The role of advanced technology in the assessment of oesophageal function in health and disease

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The role of advanced technology in the assessment of oesophageal function in health and disease

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St Thomas' Hospital

Oesophageal lab

King's College London

For Ursula and Malek

With thanks also to my parents,

Rajai and Laila

STATEMENT OF ORIGINALITY

I, Rami Rajai Sweis, confirm that the work presented in this thesis is my own. Any contribution made to the research by colleagues, with whom I have worked at St Thomas' Hospital or elsewhere during my candidature, is fully acknowledged.

I declare that this is a true copy of my thesis, including any final revisions, as approved by my thesis committee and the Graduate Studies office, and that this thesis has not been submitted for a higher degree to any other University or Institution.

Abstract

Introduction

In the absence of disease on endoscopy and failure to respond to empirical therapy, guidelines recommend manometry and reflux studies; however these investigations often fail to establish the physiological basis of oesophageal symptoms or guide therapy. Advances in technology may help provide insight into oesophageal function in health and disease and in turn direct management. The aim of this thesis was to explore the impact of introducing novel techniques and methodology through High Resolution Manometry (HRM) and prolonged wireless pH monitoring (Bravo).

Methods:

Bravo

Study 1: 110 patients who successfully completed standard catheter-based pH monitoring (C-pH) were compared with 134 patients who failed the study and progressed to 48 hour Bravo. The total reflux time (TR; total % time pH drops below 4) was used as the diagnostic marker of reflux disease. Visceral sensitivity was assessed by Symptom Index (SI) and tolerability was measured with a questionnaire.

Study 2: 38 patients who continued to have symptoms of reflux despite negative results with C-pH progressed to prolonged Bravo. 'Worst day' and 'Average cumulative' 24, 48, 72 and 96 hour Bravo measurements were compared to standard 24 hour C-pH.

High Resolution Manometry (HRM)

23 asymptomatic volunteers who underwent HRM were compared to 18 patients presenting with oesophageal symptoms. Measurements of swallow responses were collected by varying workload on the oesophagus (changing bolus volume, consistency and patient position). Normative values from healthy subjects were formulated and were used to investigate patients. A novel dysmotility-symptom association parameter (Dysfunction Symptom Index; D-SI) was formulated. Clinical outcome and final diagnosis were documented at 2 years.

Results

Bravo

Study 1: 76% of patients had a pathological TR on day 1 or 2 compared to 49% of C-pH ($p<0.01$). There was no difference in SI ($p=0.28$). A questionnaire demonstrated a preference for Bravo with reduced restriction, discomfort and dysphagia.

Study 2: Using 'Average' and 'Worst-day' analysis, 61% and 76% patients were diagnosed with reflux disease based on either pathological acid exposure or reflux-symptom association at 96 hours. Of 12 patients who underwent anti-reflux surgery, 10 (83%) reported a good outcome at 2 years.

HRM

In health contractility and coordination improved with increased workload; from upright to supine and single liquid to solid swallows. Inter-observer agreement was high and normal values were formulated. Compared to healthy subjects, meal consumption was associated with more ineffective swallows in patients (28% vs. 51%; $p<0.001$). No symptoms occurred with single water swallows. With the test meal 50% of patients exhibited symptoms and 75% of these had a pathological D-SI. Furthermore, compared to water alone, 67% patients had a manometric change in diagnosis during the test meal. 2 year follow-up studies suggest that these techniques may help guide management

Conclusion

Bravo

Tolerance, satisfaction and diagnostic yield was high in those who underwent Bravo. Prolonged pH measurement also increased the diagnostic yield in patients in whom an initial catheter study was negative.

HRM

The introduction of novel metrics and a protocol that mimics normal eating and drinking was more likely to identify the culprit dysmotility and associate these with symptoms.

In summary, these studies advance the utility of modern technology in oesophageal testing and appear to guide clinical management.

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Abbreviations

GORD	Gastro-oesophageal reflux disease
LOS	Lower oesophageal sphincter
iLOS	intrinsic lower oesophageal sphincter
cLOS	Diaphragmatic crura
OTC	Over the counter
NO	Nitric oxide
Ach	Acetylcholine
LOSR	Lower oesophageal sphincter relaxation
TLOSR	Transient lower oesophageal sphincter relaxation
SLOSR	Swallow-induced lower oesophageal sphincter relaxation
EO	Erosive oesophagitis
ENRD	Endoscopy negative reflux disease
FH	Functional Heartburn
LPR	Laryngopharyngeal reflux
MII	Multiple intra-luminal impedance
pH	Measure of acidity
MII-pH	Impedance-pH monitoring
C-pH	Catheter-based pH monitoring
NICE	National Institute for Clinical Excellence
e-sleeve	Electronic sleeve
STP	Spatiotemporal plot
PIP	Pressure inversion point
IRP	Integrated relaxation pressure
IBP	Intra-bolus pressure
CFV	Contractile Front Velocity
DCI	Distal contractile Integral
HH	Hiatus hernia.
PTZ	Proximal transition zone
SCJ	Squamo-columnar junction
DOS	Diffuse Oesophageal Spasm.
MWS	Multiple Water Swallows
PPI	Proton Pump Inhibitors

EoE	Eosinophilic oesophagitis
F	French
cc	Centimetre cubed
g	Grams
cPois	Centipoise
ml	Millilitre
Kcal	Kilocalorie
hr	Hour
PC	Pearson’s coefficient
CV	Coefficient of variation
MW	Mann-Whitney test
HB	Heartburn
R	Regurgitation
CP	Chest pain
UR	Upright reflux
SR	Supine reflux
UL	Upright liquid
US	Upright solid
SL	Supine liquid
SS	Supine solid

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Chapter 1

Background, Aims and Objectives

1.0 Background

In health the oesophagus coordinates the transport of food and fluid from the mouth to the stomach while the oesophago-gastric junction (OGJ) acts as a gateway to allow passage of bolus and limit the inappropriate reflux of gastric contents. The OGJ does not act as a one-way valve; its dynamic nature also permits venting of gas (e.g. belch) and solids (e.g. vomit) where it is appropriate. The normal oesophagus is able to clear any remaining food and fluid residue quickly and efficiently. In harmony these processes limit contact of the bolus, acid and other chemicals with oesophageal mucosa. Disruption of this highly complex muscular motion and OGJ integrity results in the interruption of food and fluid delivery and/or gastro-oesophageal reflux. Symptoms produced may range in severity from mild heartburn and regurgitation to pain and dysphagia.

1.0.1 Gastro-oesophageal reflux disease

The Montreal Definition of gastroesophageal reflux disease (GORD) was developed by an International Consensus Group based on a systematic review of the literature (Embase, Cochrane trials register, Medline) from 1980 to 2006 in adults.[1] This guideline is now used as a basis for prioritising research and permits a broad consensus among different regions of the world. It also clarifies and simplifies the classification for the diagnosis of GORD, Barrett's oesophagus, as well as extra-oesophageal disorders. (Figure 1.1) For the purposes of this thesis, only patients in whom Symptomatic Oesophageal Syndromes (Typical Reflux and Chest Pain Syndromes) were the primary presenting complaint were included in the assessment of GORD.

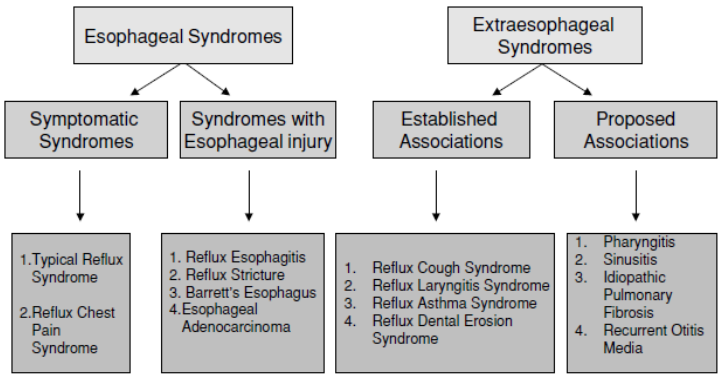


Figure 1.1 Montreal Classification. The overall definition of GORD and its constituent syndromes. [1]

Symptoms associated with Typical Reflux and Chest Pain Syndromes occur when gastric contents pass into the oesophagus at an increased frequency, are not effectively cleared or are sensed in an exaggerated manner. This can lead to mucosal damage and/or the perception of symptoms at varying degrees of severity.[2]

GORD is one of the most common health problems of the modern Western world and its prevalence is increasing.[3] Symptoms caused by GORD have an important impact on morbidity and quality of life.[1,2] GORD is associated with reduced work productivity and absenteeism.[4-6] European studies have shown that it can also be associated with an average monetary loss of €55–273 per patient per week.[4]

Overall, treatment for GORD accounts for among the largest pharmaceutical expenditures on healthcare resources.[5,7]. The use of over the counter (OTC) medications is high in this group of patients.[5,8,9] In the 2000 Gallup Study of Consumers' Use of Stomach Relief Products, 36% of patients with GORD took OTC non-prescription medication, and 56% of those with prescribed acid reducing medication also continued to take OTC drugs for break through symptoms.[10]

10-20% of the UK population have symptoms of reflux at least once per week.[11] In 2000, a community survey in the UK reported that the prevalence of reflux symptoms in adults was 29%. There was no difference between sex and age but GORD was more common in poorer communities.[12] Approximately 25% of those with GORD sought medical attention. Of those 20% were 20–29 years of age and 45% were 60–69-years of age suggesting that more patients visited their doctor as they grew older.[12] Interestingly socioeconomic status, sex and presence of irritable bowel syndrome did not influence the likelihood of seeking help, but the presence of nocturnal symptoms, and increasing the burden of co-existing upper GI symptoms (dyspepsia, nausea, vomiting and dysphagia) did.

Apart from the typical symptoms of heartburn, other presentations include chest pain, dysphagia, chronic cough, hoarseness, laryngitis, as well as ear and nose problems.[1,13] Furthermore chronic reflux is related to the rising incidence of oesophageal adenocarcinoma, especially in those with Barrett's columnar-lined oesophagus.[14]

Oesophageal cancer has increased more than any other common cancer with a 6-fold rise since the 1980's.[2]

Ambulatory reflux monitoring is essential in the investigation of patients presenting with symptoms suggestive of reflux, especially those who do not achieve symptomatic relief to acid reducing medication. Studies have shown that presenting symptoms are an unreliable guide to identifying oesophageal dysfunction and emphasize the need for objective testing in order to avoid inappropriate medical and surgical therapy.[15] An early study by Klauser et al[16] looking at presenting complaints of 304 patients with GORD symptoms showed that if either heartburn or acid regurgitation was the predominant complaint, specificity for GORD was high (89% and 95%, respectively) but sensitivity was only 38% and 6% respectively. Furthermore a poor description of presenting symptoms made it impossible to identify the predominant complaint in more than 30%.

1.0.2 Dysmotility

Oropharyngeal dysphagia refers to a disturbance in the passage of food or fluid from the mouth to the oesophagus and is the 'perception' that there is an impediment to the normal passage of swallowed material. Very few studies report the prevalence of dysphagia in the community. Of 2200 residents between 25 and 74 years of age in Olmstead County, Minnesota, the overall prevalence of dysphagia was 13.5%.[17] In one study of 313 patients in a primary care setting over the age of 62, up to 7% had dysphagia.[18] Motility disorders of the oesophagus are much less common than reflux disease, but can lead to significant morbidity and reduced quality of life including food fear, anxiety during meals and avoidance of eating in public.[19,20] Left untreated severe dysphagia can lead to dehydration, malnutrition and respiratory infections.[19,20] The elderly, in particular are at an increased risk of developing dysphagia[21] and life-threatening aspiration pneumonia.[22]

It is often difficult to differentiate symptoms of dysmotility from GORD as symptoms may be similar, dysmotility could be a consequence of chronic reflux or it may contribute to the pathophysiology of GORD.[23] Of the 2200 Olmstead County residents, 30% of patients with GORD had dysphagia compared to only 4% of those

without GORD.[17] Kahrilas et al. found that 25% of patients with mild oesophagitis and 48% of those with severe oesophagitis had peristaltic dysfunction.[24] Furthermore studies have shown improvement in peristaltic activity following successful anti-reflux surgery.[25] On the other hand, 38-75% of patients with achalasia (the most common and widely studied primary motility disorder) also have symptoms of heartburn,[26-29] and the majority have received PPI therapy to erroneously treat presumed GORD by the time they were referred.[30] Often the description of dysphagia in achalasia is vague and the classic description of dysphagia to solids and liquids is illustrated in only 75% of patients.[31] Furthermore, pathological oesophageal acid exposure has been identified in up to 20% of patients with achalasia.[32] In this group, abnormal pH studies are not usually a consequence of true acid reflux. Rather food stasis of consumed acidic foods or fluids mimic GORD; isolated prolonged episodes where the pH drops below 4 on pH studies occur as passage of food through the tight sphincter is impeded.[29] (Figure 1.2) Furthermore, fermentation of bacteria in food residue can lead to lactic acid production which contributes to heartburn and pain and can be difficult to differentiate from severe GORD.[33]

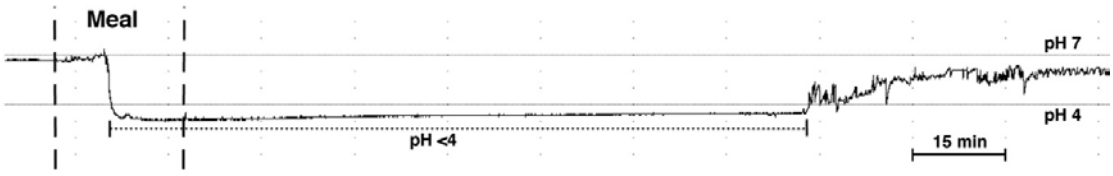


Figure 1.2 Ambulatory pH measurement in a patient with achalasia. A prolonged episode showing a pH<4 occurred due to stasis of acidic food within the oesophagus. (Reproduced from Kessing et al. CGH 2012.[32])

Therefore in most patients who present to the oesophageal lab, both dysmotility and reflux symptoms should be investigated simultaneously, and results of one should always be taken in context of the other. Even then, the diagnosis is dependant on the usefulness of the investigative tools available, the methodology used and the experience of the examiner in interpreting these results.

1.0.3 Advanced technology

Understanding the pathophysiology of GORD and oesophageal dysmotility requires a detailed analysis of the dynamic structures of the oesophagus and LOS; however description of these structures is dependant on the reliability of the tools at hand. Limitations of the current standard used to investigate GORD and dysphagia are as follows:

1. 24 hour catheter-based pH monitoring is normally used as the first line investigation for GORD; however it is not easily tolerated, it can reduce reflux-provoking activities and often misses events which do not occur during the short period of study.
2. Conventional manometry (4-8 sensors; water-perfused or solid state) is the standard tool used to investigate dysmotility; however it has very poor spatial resolution, it provides a very basic assessment of the LOS and it does not reflect true 'physiological' swallowing behaviour.

This thesis aims to investigate the use of novel and advanced technology to better understand the physiology of the oesophagus and LOS in health and disease in order to provide the opportunity for optimal medical or surgical management. Specifically, the systems that will be addressed are:

1. Bravo pH monitoring; a wireless ambulatory system used to investigate GORD over a prolonged (>24 hour) period

and

2. High Resolution Manometry; an advance in the assessment of oesophageal motility which incorporates a catheter with 36 sensors. This provides improved anatomical and spatial resolution and (in this thesis) can also be adapted for use in a novel, more physiological and functionally relevant manner where the emphasis is shifted towards reproducing patient symptoms.

1.1 Normal Adult Oesophageal Anatomy

The oesophagus is a muscular tube of approximately 25 cm connecting the pharynx to the stomach. Anatomically the cervical oesophagus (approximately 5 cm) extends from the crico-pharyngeus and the thoracic oesophagus terminates at the hiatal canal near the level of the 10^{th} thoracic vertebrae where it flares into the gastric fundus. The intra-abdominal oesophagus (usually 1–2 cm) can vary in length depending on the presence/absence of a hiatus hernia. Functionally the LOS is identified manometrically by a high pressure zone between the distal oesophagus and gastric cardia.

Similar to other parts of the gut, the oesophageal wall is histologically comprised of the mucosa, submucosa and muscularis mucosa. The length of the normal oesophageal body is lined by non-keratinised stratified squamous epithelium (with very few secretory glands). This joins with the glandular gastric columnar epithelium at the distal oesophagus as an abrupt transition (the anatomical Z-line). This can be the site of mucosal change associated with chronic reflux and oesophagitis of various stages of severity and/or Barrett's oesophagus (a pre-malignant condition associated with the replacement of normal squamous epithelium with metaplastic columnar-lined epithelium.[34])

The muscularis propria of the oesophagus consists of the outer longitudinal and inner circular muscle layers. Although these function as a single unit, the musculature is divided into the proximal striated muscle (approximately 5.5%) and the mid/distal smooth muscle (approximately 60%) which are separated by a 4-5 cm transition at the level of the aortic arch comprised of both striated and smooth muscle (approximately 4.5 cm distal to the crico-pharyngeus muscle).[35] This naturally occurring area generates the weakest force of peristaltic contractions. In some, an abnormally wide transition zone can be associated with recurrent bolus retention and dysphagia and can therefore be a target for therapy.[36] (Figure 1.3) In 2008, Ghosh et al showed that 14/25 patients with increased proximal transition zone length and duration had dysphagia.[37]

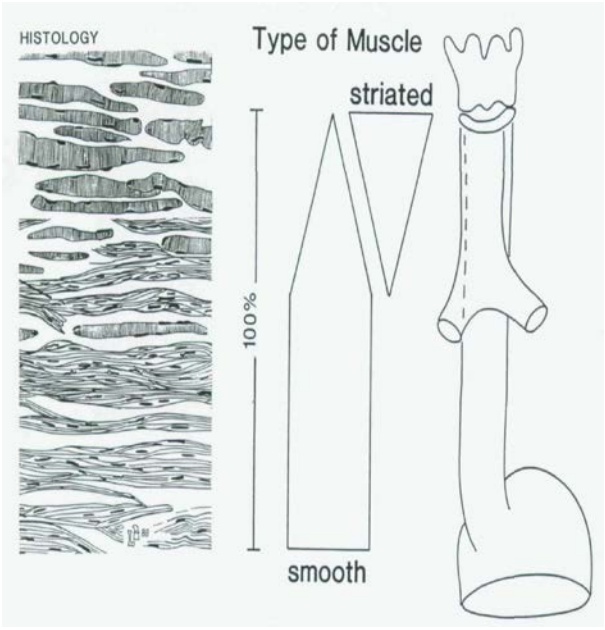


Figure 1.3 Proximal transition zone. An area of transition from striated muscle to smooth muscle in proximal oesophagus.
(Reproduced from Guili R, et al. Libbey Enrotext 1991[38] page 455-6.)

1.2 Oesophageal Motility and GORD

Swallowing initiates a highly coordinated complex sequence of events that permits the transport of the bolus from the mouth to the stomach. Voluntary swallowing initiates a pharyngeal contraction as well as 'deglutitive inhibition' of the smooth muscle oesophagus and LOS. In the striated muscle (cervical) proximal 1/3 of the oesophagus peristalsis is centrally mediated and is a consequence of sequential activation of the lower motor neurons (recurrent laryngeal vagus nerve) whose cell bodies are located in the nucleus ambiguous. The main excitatory neurotransmitter is acetylcholine (ACh) which acts on nicotinic cholinergic receptors. The most proximal portion of the striated cervical oesophagus is activated first and is followed by a sequential activation of neurons innervating more distal striated muscle levels.[39]

In the smooth muscle portion of the oesophagus (distal 2/3), inhibitory (relaxatory) and excitatory (contractile) motor myenteric neurons are innervated by separate sets of pre-ganglionic fibres which originate from the dorsal motor nucleus of the vagus. These synapse with postganglionic intramural neurons located in the myenteric plexus located between the circular and longitudinal muscle layers of the oesophagus. Pre-

ganglionic neurotransmitters are cholinergic (ACh) for both inhibitory and excitatory neurons while post-ganglionic neurotransmitters within the plexus differ: [39]

1) Inhibitory neurons release nitric oxide (NO) which inhibit contraction of the circular muscle layer by increasing the latency of contraction. This mechanism has its largest effect distally
2) Excitatory neurons release acetylcholine (ACh) which mediates contraction of both the circular and longitudinal muscles. This mechanism has its largest effect proximally.

Studies looking at the latency of contraction have shown that inhibitory innervation of smooth muscle produces a more prolonged latency distally in a sequential manner.[40-42]

Therefore with initiation of a swallow inhibitory (predominantly nitroxinergic) neurotransmitters provoke an immediate relaxation of the entire oesophagus and LOS (deglutitive inhibition) which allows the bolus to pass through the oesophagus with minimal resistance.[43-45] This inhibition does not last as long in the proximal as in the distal oesophagus. The subsequent excitatory (predominantly cholinergic) activity[43] produces a wave of smooth muscle excitation which results in a progressive, 'peristaltic' contraction with distal latency.[45]

Myenteric interneuron afferents also detect the presence of bolus as their afferent endings act as specialised sensors (mechanoreceptors and chemoreceptors). These produce an intrinsic response in which circular muscle contracts above (cholinergic) and relaxes below (nitroxinergic) the bolus. When well coordinated, effective clearance of the bolus is achieved in 5-10 seconds. Any disruption in this process may lead to bolus retention and symptoms.[36,46]

Normal peristalsis activity can involve two mechanisms: [47]

1. Primary peristalsis; a centrally mediated response which is initiated by the voluntary swallow. Food which remains in situ distends the lumen and induces a secondary peristalsis.
2. Secondary peristalsis; a peripheral response mediated by local neural reflexes.

Peristalsis is also required to clear the reflux of gastric contents which also involves primary and secondary mechanisms. Using manometry combined with videofluoroscopy, Kahrilas et al showed that even at low distal oesophageal peristaltic amplitudes of 20 mmHg, a single well-coordinated peristalsis activity will successfully clear a barium bolus.[48] This highlights the importance of coordinated peristaltic activity in clearing the swallowed or refluxed bolus despite minimal contractile pressures.

1.3 The Anti-reflux Barrier

The oesophagus and stomach span two opposing pressurised environments divided by the diaphragm. At rest, most of the oesophagus lies in the negatively pressurized thorax (approximately -5 mmHg) while the lower 1-2 cm lies within the positively pressurised abdomen (approximately +5 mmHg). Therefore theoretically, if it were not for the anti-reflux barrier at the oesophago-gastric junction, the pressure gradient across the diaphragm should lead to back flow of gastric contents.

Anatomically the OGJ is comprised of three distinct anatomical components which together form an effective reflux barrier: intrinsic LOS (iLOS), diaphragmatic crura (cLOS) and the clasp and sling muscle fibres of the proximal gastric cardia.[49] The competence of the sphincter is determined by the integrity and overlap of the intrinsic and diaphragmatic sphincters. A wide separation between the iLOS and cLOS forms a hiatus hernia, contributes to LOS weakness and increases the frequency of transient relaxations. These in turn may increase susceptibility to reflux events. New and advanced technologies can delineate these components more clearly, and abnormalities associated with incompetence of the reflux barrier can be better appreciated. OGJ disruption may predispose to an increased gastro-oesophageal pressure gradient as a result of the higher intra-abdominal pressure. This can occur with obesity,[50] with degradation of the OGJ as seen with increased age[51] and hiatus hernia.[52]

1.3.1 Lower Oesophageal Sphincter

The oesophageal body is phasic in nature and contracts transiently only upon nerve stimulation. The LOS is tonic in nature; it exhibits a continuous resting (basal) tone and relaxes on stimulation of the intramural nerves. The vagus nerve exerts both inhibitory and excitatory effects on the LOS. Basal tone is dependent on 3 factors: myogenic tone, inhibitory nitroxinergic nerves and excitatory cholinergic nerves. Relaxation of the LOS starts within seconds of swallowing (deglutitive inhibition) and is mediated by the vagal inhibitory pathway and the release of nitric oxide at the initiation of swallow. This is followed by a slightly delayed and slow activation of the excitatory motor neurons.[39] If neuronal activity is lost (eg. achalasia or vaogtomy) the unopposed myogenic tone renders the LOS in a continuous pressurised state.

The LOS cannot be identified anatomically; however its sphincter-like properties (basal tone) can be detected manometrically as a high-pressure zone in the distal oesophagus proximal to the gastric cardia. In the absence of a hiatus hernia the OGJ (iLOS + cLOS) is 1-4 cm in length and spans the diaphragm. Anatomically the iLOS is located 1-1.5 cm proximal to the squamo-columnar junction.[53] In health, its resting basal tone is reduced during deglutitive inhibition (swallowing), transient lower oesophageal sphincter relaxations (TLOSR), belching and vomiting. LOS pressure can vary in the same individual at different times[54] as it responds to changes in posture[55,56] during and after meals.[57] Furthermore activities which increase the intra-abdominal pressure and gradient across the diaphragm (i.e. abdominal compression, bending forward, straining and coughing) and those which drop the intra-thoracic pressure (sniffing, hiccoughing and deep breathing) also lead to a rise in the LOS pressure.

The length of the LOS, and in particular its intra-abdominal component, is related to the intra-gastric pressure and linked with the development of reflux disease.[58] DeMeester et al showed that a low LOS basal pressure (<5 mmHg) and/or a short intra-abdominal segment (<1 cm) increases the incidence of GORD.[59] This is most relevant with increasing age and weight and is associated with pathological supine reflux.[51]

The concept of spontaneous lower oesophageal sphincter relaxation (LOSR) was first introduced by Dent in 1976 with the development of the manometry sleeve device (a 5-6 cm sleeve that measures the maximum resting pressure within the LOS but is not affected by small displacements of the catheter).[60] In health, physiological LOSRs can occur spontaneously (transient LOSR; TLOSR) in response to gastric (postprandial) distension[56,61] and bloating resulting in a belch.[2,62] It can also follow primary or secondary peristaltic activity (swallow-induced LOSR; SLOSR). TLOSRs usually occur within 5 sec from resting pressure and can last between 5 and 40 sec,[63] or longer during SLOSRs.[64] They are thought to be triggered by mechanoreceptors within the proximal stomach which stimulate abdominal vagal afferents.[39,65] TLOSRs occur very infrequently in the supine position.[66]

TLOSRs are the most frequent mechanism of reflux and are proposed to be the only method by which reflux events occur when LOS pressures are not compromised.[62] Patients with GORD do not have an increased frequency of TLOSRs compared to healthy controls,[67] and indeed TLOSRs contribute to reflux events in asymptomatic individuals.[63,68] (Figure 1.4) Those with mild/moderate GORD do not necessarily just have increased TLOSR frequency,[69] and not all TLOSRs are associated with reflux.[70] What differs is that the frequency and volume of acid reflux during TLOSRs is greater in those with GORD than healthy controls.[67] Furthermore, disruption of the structure and function of the OGJ can compromise its integrity and contribute to the mechanism of reflux during these events. It is important to note that GORD is not only a result of increased reflux episode frequency but also of impaired clearance.[71-73] Therefore with progression of OGJ disruption, the likelihood of reflux events occurring during TLOSRs increases, as does the volume and stasis of the refluxate. (Figure 1.4)

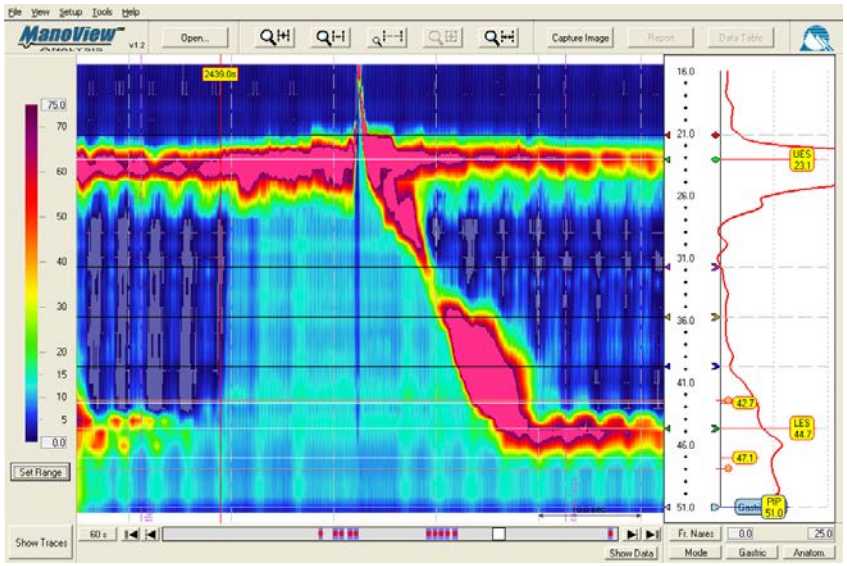


Figure 1.4 Transient lower oesophageal sphincter relaxation (TLOSR). The LOS relaxes spontaneously and is followed shortly after by a 'common cavity' during which there is equalisation of pressure between the oesophagus and stomach. The axial pressure plot (right) portrays the pressure dynamics at the position of the vertical red line on the trace (centre). This shows that the pressure below the diaphragm is greater than above. Gastric contents are therefore likely to flow down this pressure gradient and reflux into the oesophagus. A primary peristalsis terminates the TLOSR and clears the oesophagus. The intra-oesophageal pressure returns to baseline levels as does the pressure gradient on either side of the diaphragm.

Images acquired by 36-channel SSI Manoscan 360.

This Image is of the oesophagus of Rami Sweis (the author) after consuming a sandwich, and was presented on the cover of GUT in 2007.

A detailed discussion of the High Resolution Manometry spatiotemporal plot is provided in section 1.5.3

1.4 Ambulatory pH studies

(Appendix 1 and 2)

Most patients with reflux symptoms do not require a pH study. Often a typical history with endoscopic evidence of erosive oesophagitis (EO) or Barrett's oesophagus or a good response to acid suppression are sufficient to establish a diagnosis (see PPI test in section 1.7). On the other hand, those with incomplete or poor response to acid suppression, atypical symptoms and in particular those with non-diagnostic endoscopy are likely to benefit from ambulatory pH monitoring, especially for those in whom the association between reflux and symptoms is uncertain. An emphasis on symptoms is essential in the overall assessment as a patient may still have GORD if the majority of typical symptoms are correlated in time with acid reflux events despite an overall oesophageal acid exposure within the normal range ('the sensitive oesophagus')[74,75]. On the other hand a negative symptom association with a pH study showing variables marginally above the normal range may not necessarily imply GORD. Differentiating those with Endoscopy Negative Reflux Disease (ENRD; Endoscopy negative, pH study positive) and Functional Heartburn (FH; Endoscopy negative, pH study negative with typical symptoms) from those whose symptoms are not due to acid reflux will have an impact on future management, especially as studies have shown that patients with a positive relationship between reflux and symptom events are more likely to respond to conservative or surgical therapy.[76,77]

Standard ambulatory investigation is normally performed using a naso-oesophageal catheter with a distal pH electrode. In order to produce reproducible results, by convention most studies are carried out in a standardised manner:

- Indications for 24 hour pH monitoring include: classic symptoms of oesophageal reflux which may or may not be refractory to acid reducing medication/antacids, atypical symptoms (e.g. globus, chronic cough) and dysphagia or those with a suspected motility disorder.

- Proximal oesophageal acid reflux or layryngopharyngeal reflux (LPR), which may be associated with chronic cough, hoarseness, dental erosions etc. can be

investigated by placing pH sensors (normally 2) at multiple levels above the LOS or with the addition of Impedance-pH monitoring (see section 1.4.2)

- An acid reflux episode, as recorded by a pH sensor, begins when oesophageal pH drops below and ends when pH rises above 4 in the absence of locally determined ranges.[78] In Impedance-pH testing, a reflux episode is defined as weakly acid if it lies between pH 4 and 7 or alkaline if the pH is greater than 7.[79] (see section 1.4.2)

- pH monitoring is commonly preceded by manometry.[33] (see section 1.5) Manometry is the most reliable method for determining the correct position for pH sensor placement. Alternatively the LOS high pressure zone has been shown to be 1-1.5 cm proximal to anatomical Z-line.[53] Knowledge of this position can be used to determine the correct placement of the catheter tip in the absence of manometry, and is especially useful during the positioning of the wireless pH capsule. (see section 1.4.3 and Methods Chapter 2)

- By convention, the distal pH sensor is positioned so that it lies 5 cm proximal to the upper margin of the manometrically determined LOS high pressure zone. As the oesophagus naturally shortens during swallow events, TLOSR and spasm, if positioned too distally it may frequently come into close proximity to the oesophago-gastric junction and may even dip into the stomach. This will lead to false positive reflux measurements[80] (reduced specificity). Conversely, a sensor positioned too proximally will underestimate acid reflux measurements (reduced sensitivity).

- pH monitoring is usually performed while off acid suppression therapy in order to provide a diagnosis and determine the severity of acid reflux. However patients could be tested while on acid reducing medication in search of breakthrough acid reflux if symptoms are refractory to therapy.[33] The latter is especially useful in Impedance-pH testing. (see section 1.4.2)

- The study should be representative of routine daily life. Patients should therefore not modify normal daily 'reflux provoking' activities and should

reproduce their normal diet in order to improve test sensitivity. Conversely, foods and fluids with inherent acidity should be avoided to prevent inclusion of invalid non-reflux related acid measurements. (Methods Chapter 2).

- All symptoms should be recorded in a diary card and/or directly onto the event marker within the digital recording device for reflux-symptom association analysis. (Appendix 2)

1.4.1 Limitations of standard pH monitoring

Limitations of standard catheter-based pH monitoring include

i) intolerance to insertion of the catheter
ii) patients may have difficulty keeping the catheter in place for the duration of the 24 hour study. Not uncommonly they may vomit or (in)voluntarily remove the catheter. It is reported that between 5 and 10% of patients are intolerant nasal catheter insertion.[51]
iii) the nasal catheter is socially embarrassing and can result in altered behaviour which may not be representative of daily life,[81,82] thereby resulting in a false negative (or positive) diagnosis of GORD. Studies that address this concept are lacking.

Reflux events and symptoms are known to have a high day-to-day variability,[83-85] especially when reflux events are infrequent and symptoms are intermittent.[86] The total percent of time pH drops below 4 within 24 hours during 2 consecutive days can vary by up to 3.2 fold. [87] Furthermore the 24 hour catheter test has been shown to have a reproducibility of only 70-80%.[76] Therefore in those with intermittent reflux or symptom events, the clinical value and diagnostic yield of the 24 hour test may be reduced.[83-85]

Nevertheless, in most centres (nationally and internationally), presently those who are intolerant to the pH catheter or are tolerant but have inconclusive results (i.e. based on very few reflux or symptoms events), have limited further investigation options as investigation often terminates with the naso-oesophageal catheter. Clearly failure to obtain a definitive diagnosis of GORD will result in inappropriate management decisions.

1.4.2 Multiple intra-luminal impedance + pH (MII-pH)

Oesophageal symptoms are often related to disturbed bolus transport rather than acid reflux.[88] Also persistent symptoms can be due to non-acid reflux despite adequate acid suppression.[77] Acid reducing medications decrease typical reflux symptoms in the majority of patients; however these do not influence the frequency or proximal extent of reflux episodes which may be weakly or non-acidic, especially in the post-prandial period.[89,90] Persistent weakly acid reflux events can continue to induce symptoms in patients taking these medications.[91,92] Furthermore acid reducing medications have no effect on the reflux of other noxious substances produced in the stomach. Specifically pepsin (a proteolytic enzyme) and bile salts retain their damaging activity in weakly acid environments and have even been implicated in severe GORD, including Barrett's oesophagus and laryngopharyngeal reflux (LPR) disease.[93] Failure of PPIs to suppress the mechanism of reflux largely explains the lack of efficacy seen for PPIs in up to 40% of patients (higher in LPR).[91,92,94] Impedance pH monitoring can be used to investigate these phenomena.

Multiple intra-luminal impedance (MII) was first introduced in 1991 to detect the flow of gas and liquid through a hollow lumen.[95] In physics, impedance is defined as the opposition to current flow, and is an inverse measurement of electrical conductance of contents within a lumen. Impedance varies with bolus conductivity: liquid bolus has high conductivity and low impedance while air has low conductivity and high impedance. Therefore the arrival of a liquid bolus will result in a rapid voltage drop of over 50% from the nadir, and the successful clearance of the bolus leads to a rapid rise of the voltage back up to baseline. The opposite occurs with the passage of gas.

A single electrode will detect bolus movement in the lumen while multiple electrodes determine the direction of this movement. Thus, antegrade (normal swallow) vs. retrograde (reflux, vomit or belch) can be differentiated with MII.

MII is an ambulatory, catheter-based test used to determine the success/failure of bolus transit and the proximal extent of the refluxate thanks to the multiple sensors that span the catheter. Furthermore it can differentiate between liquid, gas and mixed

liquid/gas content of swallowed or refluxed material. MII has been shown to be reproducible especially for gas and mixed reflux events.[96]

MII is usually combined with a pH sensor (Impedance-pH; MII-pH) to determine whether the refluxate is acidic (pH<4), weakly acidic (pH 4-7) or weakly alkaline (pH >7);[79] an advance on ambulatory pH monitoring. It is considered the most sensitive method for reflux detection and is theorised to improve diagnostic yield by 15-20% in experienced hands.[91,97,98] Indications for its use are the same as for 24 hour pH studies (see section 1.4 above), and it is often also used in the assessment of atypical disease (e.g. LPR, aerophagea). MII-pH is also important in the detection of post-prandial reflux (often non-acidic and not accurately measurable with standard pH studies), and while on acid-reducing medication (as inhibition of acid does not alter the mechanism or frequency of reflux episodes but can still contribute to mucosal damage and symptoms).[99-101]

Nonetheless, MII-pH is currently not recommended by the UK National Institute for Clinical Excellence (NICE) as a first line investigation for GORD. NICE guidelines published in August 2004 [102] and BSG guidelines in 2006 [78] did not include MII-pH due to the paucity of good quality studies available at that time. MII-pH is also more costly, and labour-intensive and requires a degree of expertise. Thus, it is not routinely available for use in many centres. Furthermore, MII-pH is another catheter-based 24 hour study and therefore suffers from the same disadvantages of any other catheter-based study (intolerance, discomfort, altered behaviour; see section 1.4.1).

In regards to studies in this thesis, MII-pH was not used. Patients in whom atypical reflux symptoms (cough, belch, sore throat) was the primary presenting complaint were not included.

1.4.3 Wireless pH Monitoring (Bravo®)

The Bravo® pH system (Medtronic, Shoreview, Minn., USA) is an innovative, endoscopically placed, catheter-free pH monitoring system (Figure 1.5; described in detail in Methods Chapter 2). It is better tolerated than the catheter-based system and is preferred by unselected patients referred for pH investigation.[103,84,104] Prolonged measurement (up to 96 hours) increases diagnostic reproducibility and is probably most suitable in patients with intermittent symptoms with wide day-to-day variability.[85,105,106]

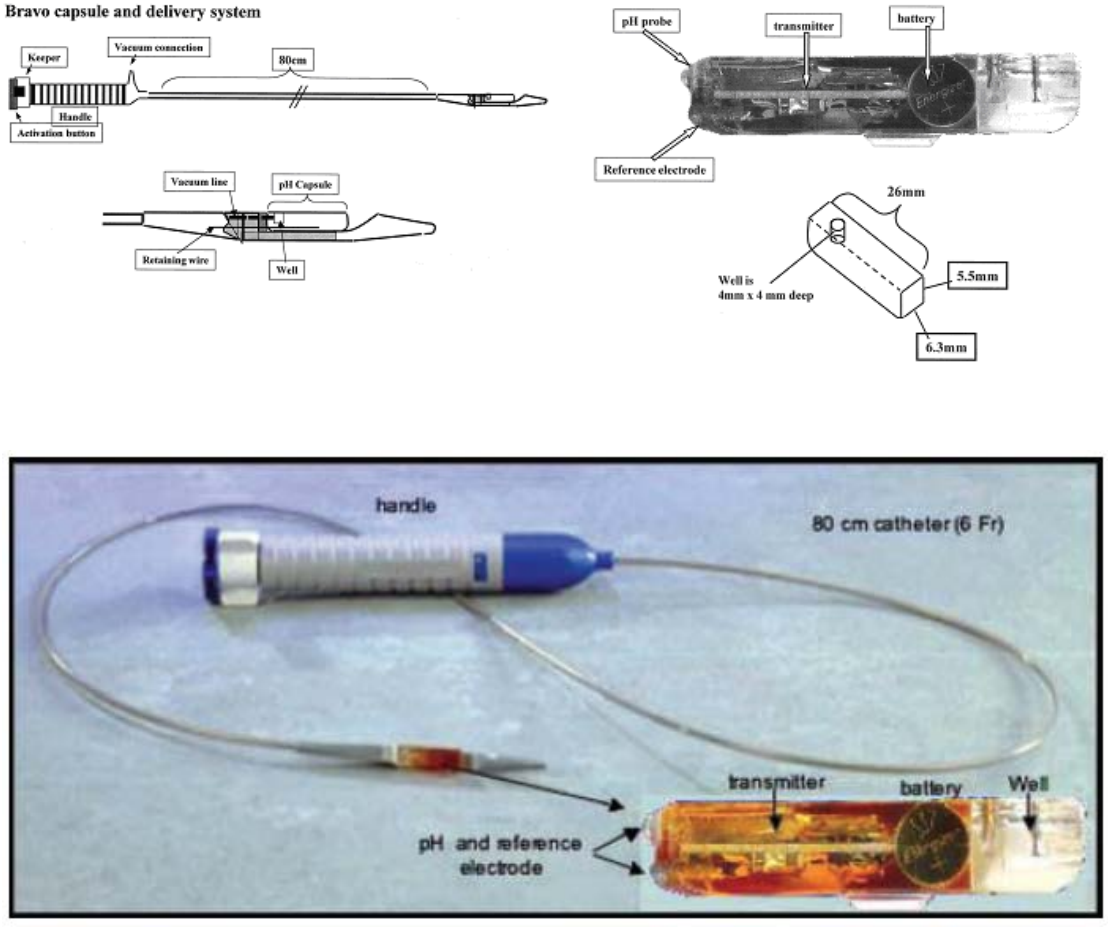


Figure 1.5 Bravo wireless pH monitoring delivery system and capsule. Process of insertion will be described in Chapter 2.

(Reproduced from Pandolfino et al Am J Gastroenterol 2003[103] and Pandolfino JE. AJG 2005[107])

Limitations of wireless pH monitoring

Bravo may be less suitable for patients with predominant post-prandial symptoms or for the investigation of patients while taking anti-secretory medications as symptoms that may arise are often associated with non-acid reflux. A study off (1 day) and on (up to 3 days) acid reducing medication has been performed in an attempt to improve the diagnostic yield of the Bravo study, especially for those in whom typical reflux symptoms do not respond to therapy;[108] however further studies are required to confirm the validity of this technique. Because of it's higher cost and the need for endoscopy during capsule placement, UK NICE guidelines state that 'wireless oesophageal pH-monitoring is most suitable for patients who do not tolerate nasal intubation' of the standard catheter.[109]

Considering the guidance from NICE, the efficacy of Bravo in the two groups of patients most commonly referred for Bravo in the UK were assessed in this thesis:

1. Patients that fail to tolerate the catheter-based system may be offered catheter-free pH monitoring (where available). Intolerance for other invasive diagnostic procedures such as colonoscopy is more common in the presence of functional gastrointestinal disease.[110] Similarly, individuals that are intolerant to the nasal catheter are often considered to have 'heightened sensitivity', functional oesophageal symptoms or psychological disease. No studies have been performed to assess factors affecting tolerance of nasal intubation and to test whether these patients have increased visceral sensitivity. Furthermore it is not known whether the diagnostic yield in terms of pathological acid exposure or symptom-association justifies further investigation with catheter-free testing.

2. Patients with typical reflux symptoms but a non-diagnostic 24-hr catheter-based investigation are often considered to have 'functional' oesophageal symptoms; however, given that 1:3 patients have a different diagnosis if the pH study is repeated on 2 separate days[51] and provided the limitations of catheter-based studies described above, a proportion may have false-negative results based on catheter-based studies and be denied appropriate therapy. Such patients are sometimes referred for wireless pH monitoring but no studies have assessed the diagnostic yield of Bravo in this group of patients.

1.5 Manometry

'The ideal manometric system would acquire continuous, high-fidelity pressure data from the pharynx to the stomach with circumferential sensitivity. The equipment should be cheap. The procedure should be quick and easy to perform and analyse. Presentation of pressure data should display not only oesophageal contractility but provide an accurate assessment of the forces that drive bolus movement, and identify (or exclude) abnormal oesophageal function as the cause of a patient's symptoms.'[111] The aims of investigation of oesophageal symptoms are to understand the patho-physiological mechanisms behind oesophageal symptoms and dysfunction, establish an appropriate diagnosis, guide rational management, and in turn improve the quality of life of the patient.

Manometry is required for the diagnosis of those with suspected motility disorders which may be amenable to medical management and is essential for those under consideration for endoscopic therapy (e.g. pneumatic dilatation, botulinum toxin injection) and surgery (e.g. anti-reflux surgery, Heller myotomy).

1.5.1 Standard Manometry

Standard manometry measures the circumferential contraction, pressure wave duration and peristaltic velocity of oesophageal swallows. Therefore it provides information regarding the peristaltic and non-peristaltic activity within the oesophagus. It is also used to assess OGJ function and position and to facilitate placement of the pH catheter probe thereafter.[33] Standard manometry is comprised of 4-8 pressure sensors which span the length of the catheter and is available either as a water-perfused or solid-state assembly. Water-perfused catheters can also incorporate a 'sleeve sensor' (Dent Sleeve) designed to provide a more stable assessment of LOS pressure during breathing and swallowing than that achieved by 'point pressure' sensors.

The Normal Swallow (as assessed by standard manometry)

A normal swallow of 5 ml of water starts with the contraction of the pharynx to propel the bolus towards the upper oesophageal sphincter which quickly relaxes. After deglutitive inhibition induces relaxation of the oesophagus and LOS, a propagated peristaltic wave helps the bolus progress down the oesophagus and the relaxed LOS permits the bolus to successfully pass into the stomach. Contraction amplitude (mmHg) is measured from the mean intra-oesophageal baseline pressure to the peak of the contraction wave. Normal amplitude values range from 30 mmHg in the proximal oesophagus to as high as 180 mmHg distally. Contraction duration is usually up to 6 seconds and is measured from the onset of the major upstroke to the end of the pressure wave. Peristaltic velocity is normally approximately 5 cm/s in the distal (smooth muscle) portion of oesophagus.[33]

In view of the natural axial movement of the LOS, a more accurate measure of sphincter pressures and relaxation was required. Dent developed a 6 cm sleeve which straddles the LOS and determines the location of the maximum pressure;[60] however this advance could only be incorporated into the water-perfused catheter which is more labour intensive and expensive.

While LOS function is of prime importance in the pathogenesis of acid reflux disease, its clinical measurement only provides an impression of (dys)function. Therefore objective evidence of GORD with ambulatory pH monitoring is always required. Manometry helps localize the LOS in order to accurately place the pH catheter tip (as described in section 1.4) as well as exclude primary motility disorders such as achalasia and diffuse oesophageal spasms which are likely to influence management.[33]

Conventional manometry classification of oesophageal pathology

Classification of pathology using the conventional manometry catheter has been revisited on many occasions.[112-114] A widely accepted definition of standard pathologies using the conventional manometry is presented below:[115]

Achalasia

Absent peristalsis with incomplete LOS relaxation

LOS basal pressure may be hypertensive *or* normal

Diffuse oesophageal spasm (DOS)

Simultaneous contractions in ≥20% of wet swallows

- with/without repetitive/prolonged/high-amplitude contractions
- with/without hypertensive resting LOS

Nutcracker oesophagus

Peristaltic waves of high amplitude (mean >180 mmHg)

Hypertensive LOS

LOS resting pressure >45 mmHg

Hypotensive LOS

LOS resting pressure <10 mmHg

Ineffective peristalsis

Low-amplitude oesophageal contractions (<30 mmHg) in ≥30% of wet swallows

Non-specific oesophageal motility disorder

Any combination of the following:

- non-transmitted contractions in 20% of swallows
- triple peaked contractions
- retrograde contractions
- isolated, incomplete lower oesophageal sphincter relaxation
- prolonged-duration peristaltic waves (> 6 seconds)

Using this classification, Dekel et al. present the distribution of oesophageal motor disorders amongst 403 patients with symptoms of dysphagia as a primary presenting complaint.[115] (Table 1.1)

Oesophageal Motility (Conventional Manometry)	
	# of cases (n=403)
Normal	53%
Hypotensive dysmotility	27%
Nonspecific oesophageal motility disorder	14%
Achalasia	18%
Nutcracker oesophagus	9%
DOS	7%
Hypotensive LOS	18%
Hypertensive LOS	7%

Table 1.1 Summary of findings from 403 patients presenting with symptoms of dysphagia using conventional manometry.
(Adapted from Dekel et al. APT 2003[115])

It is interesting to note from Table 1.1 that just over half (53%) of all patients studied had no identifiable pathology. It is unclear if this is indeed the case or if the tools and methodology used to investigate these patients played a role in reducing the sensitivity and specificity of recognising more subtle (or major) dysmotility.

1.5.2 Limitations of standard manometry

Standard manometry is readily available, is inexpensive and is the most commonly used method for measuring motor function and identifying motility disorders of the oesophagus;.[111] however it has several downfalls:

i) During a 24-hour period more than 1000 - 2000 peristaltic swallows occur with a wide variety of pressure events as normal eating and drinking behaviour ensues. Therefore many intermittent motility abnormalities are missed using the standard ten swallows of 5 ml of water.

ii) With only 4-8 pressure sensors the ability of standard manometry to predict effective bolus transport is limited by poor spatial resolution. Segmental or focal abnormalities within the oesophagus, (wide break in

contractility, focal hyper/hypo-peristalsis, segmental spasm) will inevitably be missed.

iii) With conventional manometry abnormalities are defined in terms of a few basic patterns: incomplete sphincter relaxations, oesophageal spasm, hypo- and hypertensive contractions and non-specific dysmotility. This classification is simple with poor inter-observer agreement in interpretation (even amongst experts) and only fair reproducibility.[116,117] Furthermore the majority of these 'pathologies' can also be found in asymptomatic individuals. Only primary motility disorders (such as achalasia and diffuse oesophageal spasm) can be diagnosed with reasonable confidence, although with recent advances in technology, even these have been re-classified.[118,119]

iv) The LOS anatomy is poorly appreciated, especially in the context of a hiatus hernia or very weak LOS. Furthermore, unless a water-perfused catheter with a Dent sleeve is used, the catheter does not take into account oesophageal shortening which may shift the LOS proximally (sometimes even above the sleeve device) therefore giving a false impression of LOS relaxation (pseudorelaxation).[119]

v) Symptoms are rarely triggered by 5 ml water swallows in the supine position of fasted patients (as is the standard protocol). Patients usually complain of symptoms during eating or post-prandially as well as during manoeuvres that increase workload on the oesophagus and/or compromise the reflux barrier (free drinking, bending forward).

1.5.3 High Resolution Manometry

The fundamentals of High Resolution Manometry were first established in the early 1990s by Clouse and Staiano[120,121] who developed a model by which a functional image of the oesophageal anatomy was generated from multiple pressure sensors on a catheter. (Figure 1.6a) This information was reconstructed into a 3-dimensional plot using time of peristalsis, distance down the oesophagus and pressure amplitude as its axes. The 3-dimensional plot was then superimposed onto a 2-dimensional image and the pressure changes were re-presented as a topographic plot. (Figure 1.6b). With the advent of micro-manometric water-perfused assemblies[122,123], and later solid state catheter assemblies[124,125] up to 21-36 sensors could be introduced, thereby considerably improving image resolution especially as changes in pressure were then assigned different colours. Therefore with its increased number of sensors and spatiotemporal representation of pressure activity, the functional segmental anatomy of the oesophagus could be appreciated. (Figure 1.7)

Ongoing progress in research, technology and advanced software algorithms have also enabled HRM to compute measurements that are key to predicting successful bolus transport and are not possible with conventional manometry. Such parameters (Intrabolus pressure, Integrated relaxation pressure, Contractile front velocity; see Classification below and Methods Chapter 2) have been linked to improved diagnostic accuracy and are presumed to improve sensitivity to dysfunction that causes symptoms and are clinically relevant to the patient.[111,126] In addition HRM can assess OGJ anatomy in greater detail and identify dysfunction that may predispose to GORD. It is important to note, however that although oesophageal pressure measurement is the most direct method for assessing motor function in the oesophagus and OGJ it is not a radiologic study and can only predict bolus transport by inference.

Such features are unique to HRM and are important as symptoms and mucosal damage are more likely to occur due to a disturbance of bolus transport and poor clearance of refluxate rather than abnormal pressure events as described by standard manometry.[111] Furthermore, an ‘electronic sleeve’ (e-sleeve), which emulates the Dent sleeve device of standard manometry, can be applied in order to provide stable

LOS measurements during analysis regardless of shifts in the catheter or patient position or of oesophageal shortening. This facilitates the positioning of the catheter and removes the need for the time-consuming pull-through technique required in standard manometry. Advantages and disadvantages of standard vs. High Resolution Manometry are presented in Table 1.2.

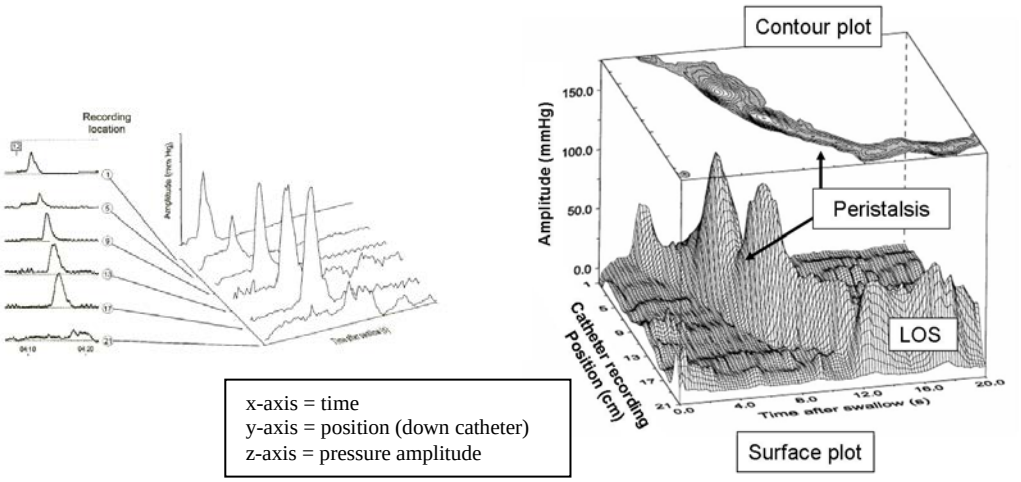


Figure 1.6a **Figure 1.6b**

Figure 1.6 2 dimensional topographic reconstruction of a High Resolution Manometry spatiotemporal plot.

a) Clouse and Staiano[127] laid the foundations for HRM: time, catheter position and average pressure were reconstructed into pseudo-3 dimensional plots.

b) The pseudo-3 dimensional surface plot displays peaks and troughs representing a peristaltic pressure wave as it progresses from the proximal oesophagus (background) to the LOS after-contraction (foreground). The contour plot of the same swallow is superimposed at the top of the figure. This demonstrates how the 3 dimensional data can be re-presented using concentric rings at 10 mm Hg intervals to depict changes in pressure.

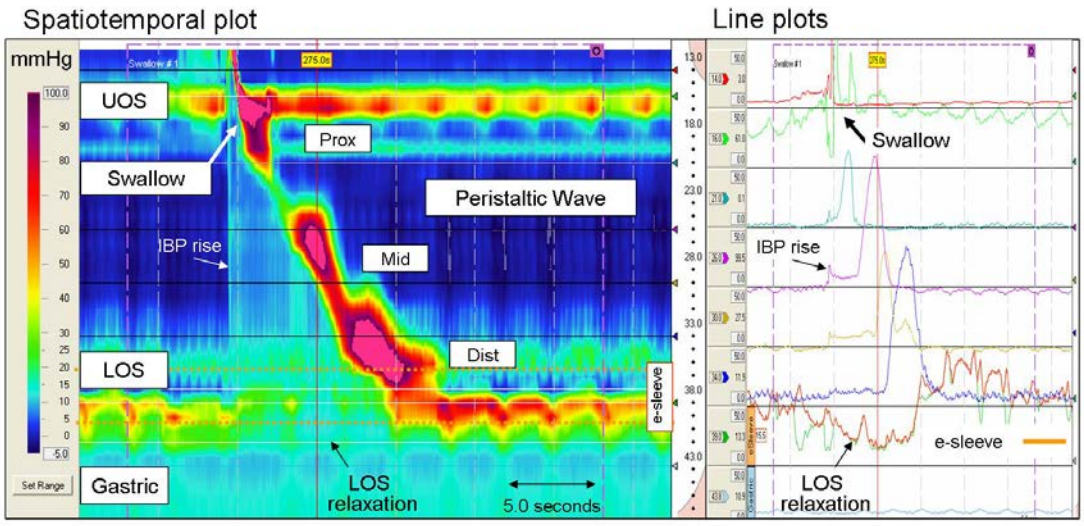


Figure 1.7 High-resolution manometry spatiotemporal plot of normal peristalsis. The trace depicts oesophageal pressure activity from the pharynx to the stomach via pressure sensors spaced at <2 cm intervals. Recordings can be analysed and presented either as line plots (right; similar to conventional manometry) or spatiotemporal plots (left). The spatiotemporal plot presents similar information as the line plots: Time is depicted on the x-axis, distance from the nares on the y-axis and amplitude on the z-axis. Pressure is represented as changes in colour (legend left). The virtual "e-sleeve" application provides measurement of LOS pressure and relaxation in the spatiotemporal plot, and is represented as brown in the line plot.

The resultant HRM trace of a normal swallow demonstrates the segmental functional anatomy of the oesophagus. Deglutitive inhibition is seen as the synchronous relaxation of the UOS and LOS. This is followed by a coordinated peristalsis with increasing pressure duration as it passes distally. (Images acquired by 36-channel SSI Manoscan 360).
(Reproduced from M. Fox and A Bredenoord Gut March 2008[126])

	Conventional pull-through manometry	Conventional sleeve manometry	High-resolution manometry
Costs	Inexpensive	Inexpensive	Expensive
Execution	Elaborate and time consuming	Elaborate and time consuming	Relatively simple and fast
Interpretation	Requires experience, simple classification	Requires experience, simple classification	Relatively simple, Changing classificaiton, Interpretation requires experience
Measuring LOS function and relaxation	Limited	Yes	Yes, detailed
Measuring UOS function and relaxation	No	Limited	Yes, detailed
Phyiological challenge swallows	Difficult to perform & interpret	Difficult to perform & interpret	Easy to perform, pattern recognition
Engages patient	Difficult to follow	Difficult to follow	Easy to comprehend & interact (therapeutic)

Table 1.2 Comparison between Conventional and High Resolution Manometry.

It is interesting to note that with HRM, the spatio-temporal plot can be easily interpreted not only by the in-experienced user but also by the patient. With a brief description of oesophageal anatomy and function (e.g. '*here is the top of the gullet, the bottom of the gullet and the beginning of stomach…and here is your swallow as it progresses down'*), patients often enjoy watching their swallow initiate, progress and terminate. This 'personal' appreciation of oesophageal function helps not only with tolerability of the test but can also be therapeutic in itself as patients can 'see' where the problem lies (or does not), and take ownership of their own disease (or be convinced of the lack thereof). This is especially important in functional pathology, such as rumination[128] (Figure 1.8), where patients often require persuading that the problem is not organic, rather it is a functional, subconscious yet learned behaviour which they can see, feel and appreciate. This interaction is often therapeutic in itself.

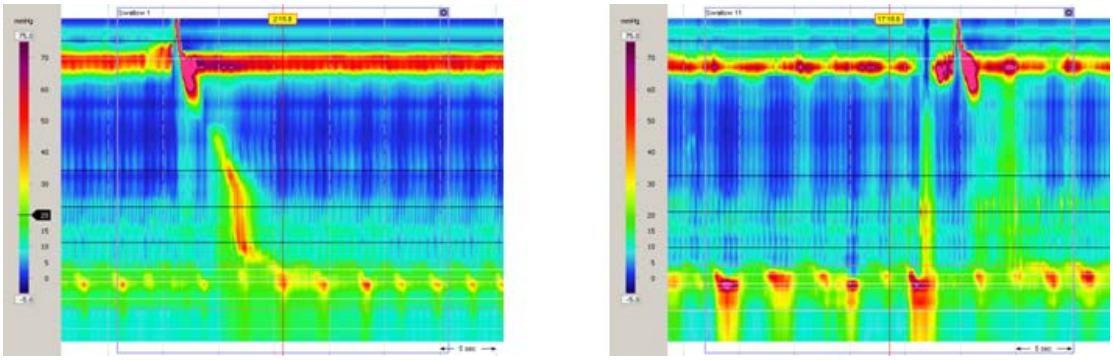


Figure 1.8 Rumination syndrome. 24 year old female final year medical student with regurgitation, vomiting and weight loss. Recurrent 'vomiting' and regurgitation was affecting her quality of life; she was unable to eat in public and she was considering postponing her medical school exams. Endoscopy was normal. There was no improvement with acid reducing medication. HRM to water swallows was normal (left panel). Following 250 ml milkshake there were episodes of sharp increases in the intra-gastric pressure with concurrent relaxation of the upper oesophageal sphincter after which the milk shake entered her mouth (right panel).
The aim of Biofeedback therapy is for diaphragmatic breathing to overwhelm the abdominal muscles and diaphragm. With perseverance, this newly learned behaviour should itself become subconscious and occur effortlessly during any rumination-provoking event.
(Reproduced from Sweis et al. Gut 2010[128])

Rumination syndrome is a benign, voluntary yet subconscious behaviour which occurs as a consequence of learned anticipation to gastric distension. Biofeedback therapy with diaphragmatic breathing provides the best prognosis. In this case following biofeedback therapy (administered by Rami Sweis) the patient's symptoms completely resolved, she gained weight and was able to complete her final medical school exams with merit.

1.5.4 High Resolution Manometry classification of oesophageal pathology

Classification of pathology using HRM has advanced the understanding of disease in the human oesophagus. This classification has been re-visited on several occasions over the last 5 years, each with a subtle advance in definitions and terminology. This process has been largely pioneered by the Chicago group at Northwestern University, USA.[129-131] This HRM classification focused on the HRM system developed by Sierra Scientific Instruments Inc. (Los Angeles, CA, USA). Normative data have been derived using the Manoscan 36 channel circumferential solid-state hardware and Manoview analysis software (Sierra Scientific Instruments Inc.) The principles of analysis were intended to generalize to any HRM system. Since studies in this thesis have been performed, two further updated versions of the classification have emerged with few subtle changes.[118,132]

The normal swallow was described in Figure 1.7. A more detailed assessment of analysis will be described in detail in the Methods Chapter 2 as well as in Chapters 5 and 6. Oesophageal bolus transport depends on the balance of resistance through the OGJ, (intra-bolus pressure; IBP) and oesophageal closure pressure behind the bolus.[133,134]

Unlike with conventional manometry, HRM classification considers the OGJ *before* the oesophageal body, with the rationale that any pathology within the OGJ will influence what happens proximally. Therefore an assessment of deglutitive OGJ relaxation and OGJ pressure morphology (i.e. presence of a hiatus hernia) need to be described first.

I. OGJ classification

OGJ relaxation

Incomplete deglutitive OGJ relaxation is an essential feature in the diagnosis of achalasia. There is no accepted method for defining *incomplete* OGJ relaxation using conventional manometry. The Chicago group have shown that the optimal parameter for quantifying this measurement is the integrated relaxation pressure (IRP).[134] IRP is defined as the ‘lowest mean eSleeve pressure for four contiguous or non-contiguous seconds within the relaxation window’. The relaxation window is a period of OGJ

relaxation that occurs after initiation of the pharyngeal swallow and terminates at the arrival of the peristaltic wave front (Figure 1.9 and Methods Chapter 2). This metric is automatically calculated by the proprietary software over 10 seconds from initiation to termination of swallow. The upper limit of normal is 15mmHg (with single water swallows). IRP has been shown to have a 98% sensitivity and 96% specificity for differentiating achalasia from control subjects, and is more accurate than the 3 second nadir relaxation pressure of previous calssifications.[134]

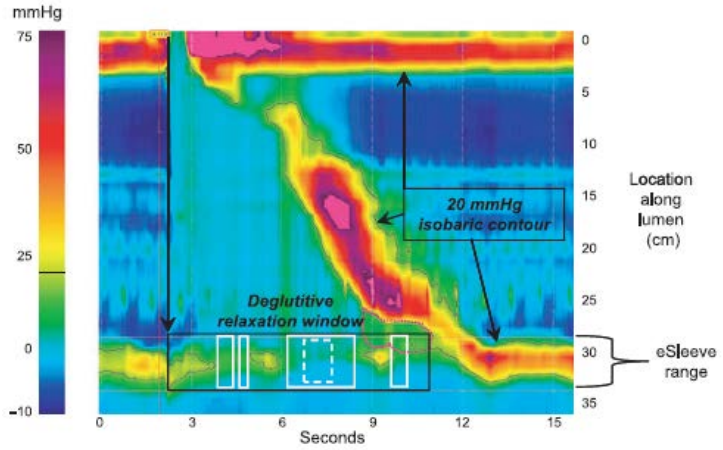


Figure 1.9 Integrated relaxation pressure (IRP). Deglutitive relaxation window (black box) within a normal swallow from which the IRP is calculated (white boxes). This differs from the 3 second nadir pressure of previous classifications (dotted white box). (Figure reproduced from Ghosh et al Am J Physiol Gastrointest Liver Physiol 2007[134])

OGJ morphology

With conventional manometry, there is little appreciation for the structural components that make up the OGJ. HRM can differentiate two sphincteric intra-luminal pressure changes: intrinsic LOS (iLOS) + surrounding crural diaphragm (cLOS) (see section 1.3.1). The cLOS component is most clearly visible in inspiration. By localising iLOS and cLOS, HRM can define three OGJ morphologic subtypes. [131] (Figure 1.10)

Type I: The 2 components overlap and there is no separation between iLOS and cLOS. This morphology is most commonly seen in healthy individuals

Type II: There is minimal but discernible separation between the iLOS and and cLOS (≤2 cm). This is defined as an intermediate condition between normal and a hiatus hernia (HH).

Type III: The iLOS and cLOS are separated by >2 cm; the HRM signature of HH.

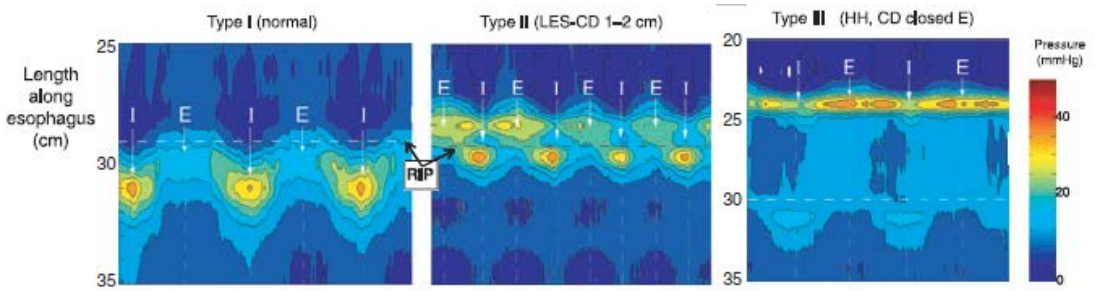


Figure 1.10 HRM with three OGJ morphologic subtypes.

Type I (normal)

Type II (≤2cm separation between LOS and crural diaphragm)

Type III (>2cm separation between LOS and crural diaphragm).

(Figure reproduced from Pandolfino et al Am J Gastro 2007 [131])

II. Oesophageal classification

Oesophageal segment contraction

(for more detailed definitions of terms please refer to Chapter 5)

A swallow is categorized first by highlighting a 30 mmHg isobaric contour which circumscribes all pressure segments within the peristaltic wave that are at or above 30mmHg. The software then calculates other HRM-specific parameters which help describe important swallow characteristics.

Intra-bolus pressure (IBP) - the compartmentalised pressure between the distal contractile segment below the bolus and above the OGJ

Contractile Front Velocity (CFV) - a measure of peristaltic velocity derived from the 30 mmHg isobaric contour as it circumscribes the distal (smooth muscle) contractile segment

Distal contractile Integral (DCI) - a measure of contractile vigour within the distal peristaltic segment

These novel metrics are essential for defining pathology in the oesophageal body and are the basis for the new HRM classification. Normal values were referenced to atmospheric pressure and the 30 mmHg isocontour. Furthermore, non-specific terminologies from conventional manometry classification such as ‘peristaltic dysfunction’ and ‘ineffective oesophageal dysmotility’ are abandoned.

I. Classification of individual swallows

- **Normal**

  <3 cm defect (break) in distal segment

  CFV < 8 cm s-1

  IBP < 15 mmHg

  DCI < 5000 mmHg s-1 cm-1

- **Hypotensive peristalsis** (Figure 1.11)

  Normal appearing peristaltic wavefront with a defect in the distal segment of ≥3cm

  (defined as ineffective oesophageal dysmotility with conventional manometry)

  Absent peristalsis (Figure 1.12)

  No propagating contractile wavefront

  <3 cm contractile activity in >30 mmHg isobaric contour

- **Hypertensive peristalsis**

  Normal appearing wavefront propagation

  DCI > 5000 mmHg s-1 cm-1

- **Spasm** (Figure 1.14B)

  CFV ≥ 8cm s-1

- **Elevated IBP** (Figure 1.14A)

  IBP > 15 mmHg

- **Pan-oesophageal pressurisation** (Figure 1.13)

  Oesophageal compression from UOS to OGJ with IBP >30 mmHg

II. Classification based on all (water) swallows during the study

Following 10 swallows of 5ml of water, classification is then divided into those with impaired OGJ relaxation and those with normal OGJ relaxation

1) Impaired OGJ relaxation - (IRP ≥15 mmHg) &/or elevated IBP (≥15 mmHg)

Achalasia (Figure 1.13)

Classic achalasia

Mean IRP ≥15 mmHg, absent peristalsis

Achalasia with oesophageal compression

Mean IRP ≥15 mmHg, absent peristalsis

Pan-oesophageal pressurization with ≥20% of swallows

Spastic (Vigorous) achalasia

Mean IRP ≥15 mmHg, absent peristalsis

Spasm (CFV >8 cm s-1) with ≥20% of swallows

Functional OGJ obstruction (See figure 1.14A)

Normal CFV

Mean IBP >15 mmHg with ≥30% of swallows compartmentalized above OGJ (suggests obstruction at the OGJ)

2) Normal OGJ relaxation (IRP <15 mmHg) and normal IBP

Absent peristalsis

100% swallows with absent peristalsis

Hypotensive peristalsis

Intermittent ≥30% of swallows with hypotensive or absent peristalsis

Frequent ≥70% of swallows with hypotensive or absent peristalsis

Hypertensive peristalsis

Normal CFV, mean DCI >5000 & <8000 mmHg s-1 cm-1

(and/or hypertensive LOS aftercontraction >180 mmHg)

Spastic nutcracker

Normal CFV, mean DCI > 8000 mmHg s-1 cm-1

Distal oesophageal spasm (Figure 1.14B)

Spasm (CFV > 8 cm s-1) with ≥20% of swallows

Segmental spasm limited to S2 or S3

Diffuse spasm involving both S2 and S3

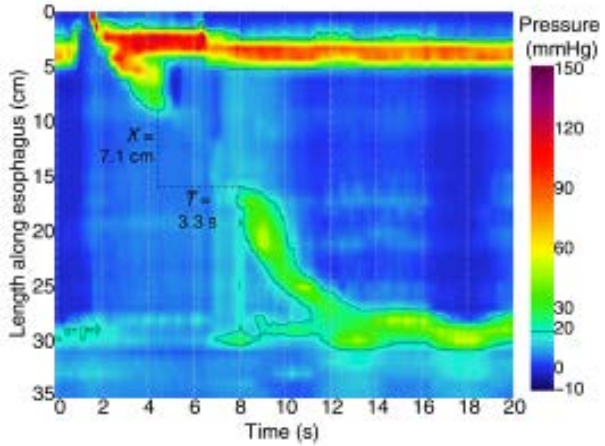


Figure 1.11 Break in peristaltic wave front of >3cm. In this case it is within the proximal oesophagus which is known as the proximal transition zone (PTZ). (Reproduced from Ghosh et al. NGM 2008[135])

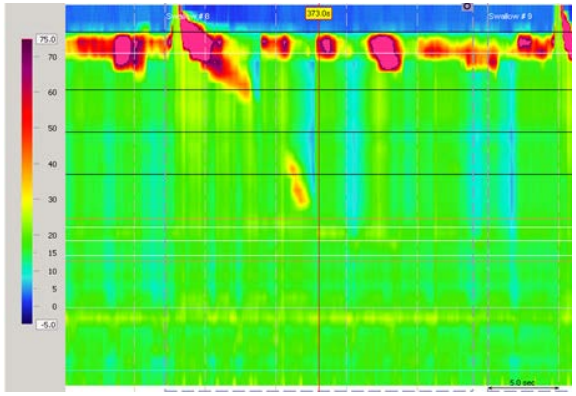


Figure 1.12 Absent peristalsis. The only visible pressure measurement identifiable within the 30 mmHg isobaric contour is <3cm in length.

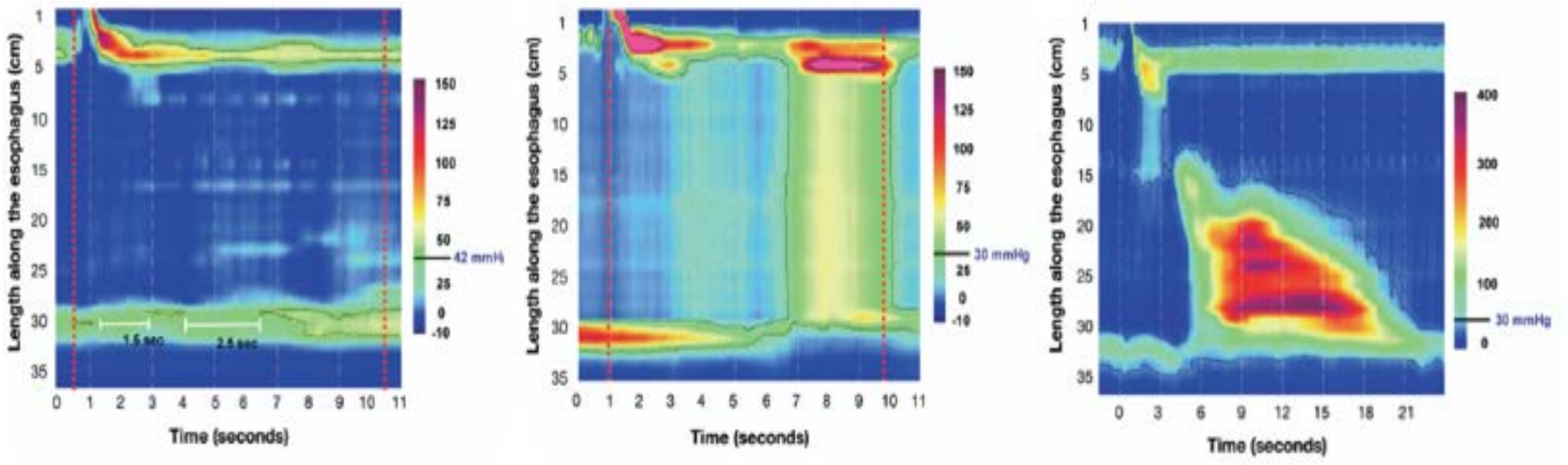


Figure 1.13 HRM achalasia subtypes. Type I, Classic Achalasia (left); Type II, Pan-oesophageal pressurisation (middle); Type III, Spastic (or Vigorous) achalasia

(Figure reproduced from Pandolfino et al. Gastroenterology 2008[136])

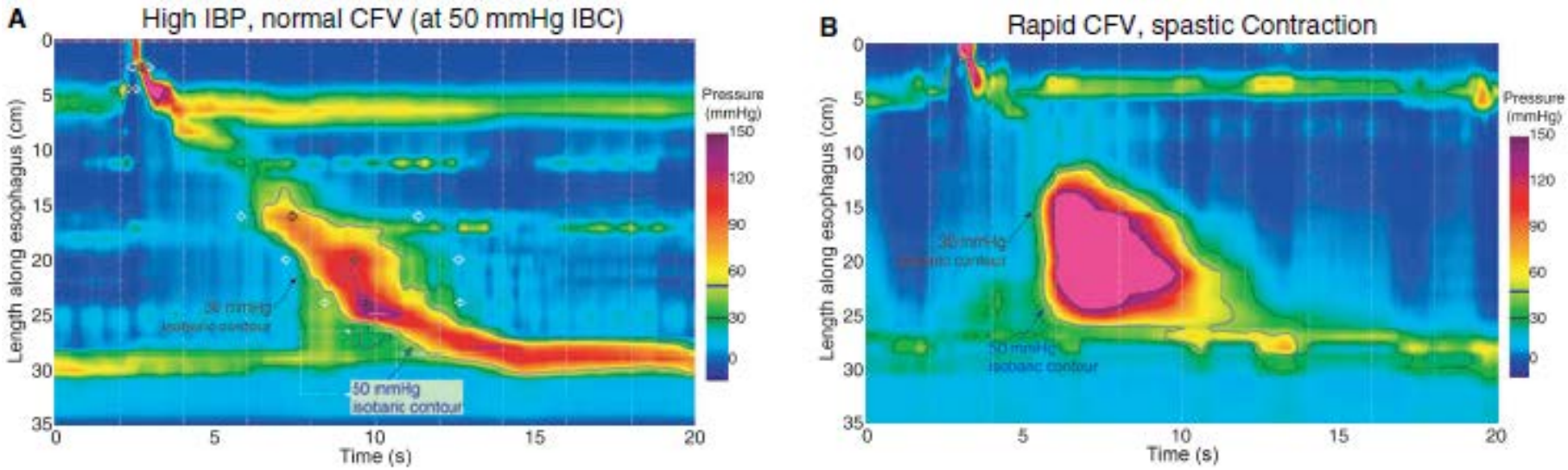


Figure 1.14 Functional OGJ obstruction vs. Diffuse Oesophageal Spasm (DOS).

A) Functional obstruction at the OGJ with raised intra-bolus pressure. B) DOS with rapid CFV is attributable to spasm as the entire distal oesophagus is contracting simultaneously.

(Figure reproduced from Pandolfino et al. NGM 2009[131])

With the introduction of this 'new' classification, Pandolfino et al presented the distribution of oesophageal motor disorders amongst 396 patients presenting with primary symptoms of dysphagia. (Table 1.3) It is in interesting to note that compared to the 403 patients in Dekel et al (Table 1.1), the Chicago group describe nearly 25% less 'normal' findings with the use of HRM. This is likely because of the improved technology, new metrics and methodology; however it is difficult not to question the accuracy of these findings. With the improved sensitivity of this technology, could 'normal' oesophageal function have erroneously been classified as 'pathology' regardless of its relation to patient symptomatology? This 'new' classification (as well as that using conventional manometry) is based on 5 ml water swallows in the supine position. This is not likely to trigger symptoms yet any apparent dysmotility event is taken into account. Unless patient symptoms are reproduced, questions remain regarding the relevance of 'disease' identified. It is on this premise that HRM studies presented in this thesis are based.

Oesophageal Motility (High Resoluiton Manometry)	
	# of cases (n=396)
Normal	**91 (23.0%)**
Hypotensive dysmotility	**73 (18.4%)**
Aperistalsis	**29 (7.3%)**
Hypertensive peristalsis	**37 (9.3%)**
Nutcracker	16 (4%)
Segmental nutcracker	12 (3%)
Spastic nutcracker	6 (1.5%)
Nutcracker LOS	3 (0.8%)
Spasm	**6 (1.5%)**
Abnormal LOS tone	**39 (9.9%)**
Achalasia	**73 (19.4%)**
Classic	69(17.4%)
Pan-oesophageal pressurisation	4 (1.0%)
Vigorous	44 (11.1%)
Functional obstruction	**44 (11.1%)**

Table 1.3 Summary of findings from 396 patients presenting with symptoms of dysphagia at Northwestern University Oesophageal lab in Chicago, USA.
(Adapted from Pandolfino et al Am J Gastro 2008130)

1.6 Introduction of physiological challenges in High Resolution Manometry studies

Studies which combine standard manometry and multiple intra-luminal impedance technology (MII) at various body inclinations and swallowed bolus viscosities (used as surrogate measures of increased workload on the oesophagus) have shown that at lower inclinations both liquid and viscous materials travel slower while the distal oesophageal amplitude increases.[137,138] Furthermore TLOSRs and gas reflux events are suppressed in the supine position in both healthy volunteers and in patients with mild-moderate reflux disease.[139] The effects of position on oesophageal peristalsis and lower oesophageal sphincter pressure assessed by conventional manometry alone have been less consistent.

HRM and video-fluoroscopy have been applied to study the effect of position and bolus consistency on oesophageal function.[57] No effect of position on LOS pressure was found in the thin, healthy volunteers used in the study. In contrast peristaltic pressure increased and velocity decreased as subjects moved from the upright to the supine position. Similarly, peristaltic pressure increased and velocity decreased progressively as subjects undertook dry, water and solid swallows respectively.[57] These observations confirm findings from studies which combined manometry and impedance studies (described above) which show that oesophageal function is not stereotyped but responds to the workload required for effective bolus clearance.[137-139]

Similar to standard manometry, HRM normal values have been established for peristalsis and the OGJ using small volumes of water in the supine position.[50,125] However, HRM can facilitate the assessment of the dynamics of swallows in different positions, food consistency (solids) and volumes. In theory, such activities should provide a better physiological assessment of swallow as they act as a stressor to the oesophagus. Understanding the oesophageal response due to 'physiological challenges' is likely to be of clinical importance because most patients complain of swallowing problems, regurgitation or chest pain during eating or drinking (i.e. increased workload on the oesophagus) and during the postprandial period. Similar techniques have been reported to improve the sensitivity of investigation for functional and structural pathology (strictures, rumination, achalasia).[126,140,141]

Therefore this is likely to have an impact on diagnostic accuracy as the emphasis is shifted from identifying abnormal pressure events (as is currently performed with standard and HRM) to inducing and targeting symptoms that are relevant to the patient and identifying dysmotility events that are related to these symptoms. However the use of physiological challenge swallows (such as drinking freely, swallowing solids and eating) have not entered routine clinical practice probably because of the difficulty in interpreting the more complex pressure activity, the absence of normative values and the lack of a standardised methodology. This challenge will be addressed in this thesis.

1.7 Management of Reflux disease and dysphagia

1.7.1 Reflux disease

Proton Pump Inhibitors (PPIs) reduce gastric acid secretion and improve typical reflux symptoms in the majority of individuals; however 10-40% of patients have a poor response.[94] The majority (up to 70%) have endoscopy negative reflux disease (ENRD; positive oesophageal acid exposure and/or positive reflux-symptom association) or functional heartburn (FH; negative oesophageal acid exposure and reflux-symptom association yet with typical symptoms of reflux). In a systematic literature review of seven trials (1854 patients), Dean et al found that the pooled response rate to once daily PPIs at 4 weeks was 37% in ENRD.[142] In contrast, those with erosive oesophagitis (EO; patients with endoscopic evidence of oesophagitis) account for only 30-40% of the GORD population;[143] however there is at least 15% discrepancy between symptom resolution and mucosal healing, and up to 50% of patients with EO in whom symptoms recur while taking a PPI show no relapse of oesophageal inflammation.[94] In large comparative studies, PPIs produced endoscopic healing in over 80% (over 90% with esomeprazole)[144] while symptomatic relief was achieved in over 56% (up to 76% with esomeprazole)[142,145] even after EO was healed macroscopically. In general, the proportion of ENRD patients responding to a standard dose of PPI is approximately 20–30% lower than in EO.[94] Therefore, distinguishing EO, ENRD, FH and those whose symptoms are not reflux-related is important to target appropriate therapy, especially if anti-reflux surgery is under consideration.

Patients with Barrett's oesophagus have more severe oesophageal dysmotility than those with other forms of reflux disease or healthy controls.[146-149] In addition, oesophageal sensitivity to (refluxed) acid is reduced and patients swallow less frequently therefore leading to delayed acid clearance.[2] This combination of motor and sensory dysfunction is linked to increased severity of acid exposure,[51] and in particular, highly prolonged reflux events that predispose to mucosal damage.[150] Patients with Barrett's who have symptoms tend to respond well to acid reducing medication. On the other hand, patients with ENRD and FH may have borderline results on ambulatory reflux studies but have severe symptoms which respond very poorly to acid suppression.[151]

A ‘treat then test’ policy has long been a standard diagnostic technique for GORD in clinical practice. In the absence of alarm symptoms, the previous paragraphs have described how PPI therapy may improve symptoms in EO and ENRD. Those with typical symptoms of heartburn and chest pain are more likely to respond to PPI than those with volume regurgitation and atypical symptoms (cough, LPR).[2,97,152,153] In 2000, Fass et al. showed that the omeprazole test is as sensitive as ambulatory pH monitoring in diagnosing GORD in patients with EO.[154] Wang et al[155] evaluated the accuracy of a using PPI treatment as a diagnostic test. They performed a computerized literature search using PubMed, MEDLINE, EMBASE, CINAHL, and Cochrane Controlled Trials Register databases for relevant articles published between 1966 and May 2004. They found that overall the PPI test had an acceptable sensitivity of 80% and specificity 74% in GORD patients with non-cardiac chest pain; however the dilemma of how to define the cause of symptoms and determine effective therapy in those with non-cardiac chest pain who do not respond to PPI therapy remains a challenge.

Apart from those with ENRD and FH, reasons for why patients may fail to respond to PPI include poor or non-complinace,[143] increased sensitivity to acid (and non-acid) refluxed material, sensitivity to distension within the oesophagus, anxiety and psychosocial stress.[143,156] Contributing pathologies include disturbed bolus clearance, oesophageal dysmotility[24] and behavioural disturbances[157] (including rumination; Figure 1.8). Before embarking on further investigations, conservative management strategies are usually considered. Compliance and adherence to PPI therapy are usually addressed first. It is advised that patients take PPI twice daily, 30 min before breakfast and dinner for maximal efficacy. If this fails, the PPI could either be doubled or changed.[158] The only real lifestyle modifications shown to have a positive effect include weight loss and elevation of the bed head.[159] Chewing gum after meals has shown promise.[160] Although there is little evidence that altering specific foods works, reducing calorie content improves reflux and symptoms while reducing fat content does not improve reflux but it does reduce symptoms by up to 40%.[161] The addition of a histamine 2 receptor antagonist (H2RA) provides a relative benefit of 41% compared to placebo and it is now common practice to introduce ranitidine before bedtime to tackle nocturnal reflux.[143] However it is suggested that the efficacy of H2RA is reduced in the long term due to development of tolerance.[162]

Alginate antacid (e.g. Gaviscon Advance) has up to 60% relative benefit compared with placebo, and is as effective as H2RA.[163] Alginate has a number of features that may protect the patient from both acid and non-acid reflux. As it is highly viscous, it forms a 'raft' that floats above the gastric contents and forms a plug which acts as a physical barrier to reflux.[164-166] Also antacids within neutralize gastric acid more rapidly than PPIs.[167] Furthermore, the alginate binds other noxious substances such as pepsin and bile, thus reducing their damaging effect on mucosa.[168,169] Alginate containing antacids are normally consumed after meals and can be used in addition to other therapies (such as PPI).

Reflux suppression can be induced with the $GABA_B$ agonist, baclofen (e.g. 5mg tds increased to 20 mg tds[170]). Baclofen is usually used as an adjunct to PPI therapy. It has been shown to reduce TLOSRs by 40-60% and reflux episodes by >40%[171] and is effective even in the presence of a HH.[172,173] Unfortunately the central side effect profile of Baclofen (e.g. dizziness, somnolence) makes it difficult for many individuals to tolerate it in the long therm.

When all else fails, or if the patient chooses not to continue long term medical therapy, anti-reflux surgery is an option that may provide a 'relatively' more permanent solution. Rosenthal et al. showed that out 143 patients, pre-operatively 88% had refractory GORD and 42% no longer wanted to continue life-long medication. In 82% the pre-operative reflux symptoms had disappeared after surgery and 94% were very satisfied with the outcome with an excellent resultant quality of life.[174] However careful patient selection is paramount. Failure evoke any response to PPI therapy pre-operatively predicts poor outcome and evidence of pathological oesophageal acid exposure on pH testing is crucial.[175] Furthermore, manometry might also help predict outcome as studies suggest that patients with a normal or raised mean LOS pressures pre-operatively are at increased risk for developing post-operative dysphagia.[176]

Therefore, in patients with symptoms suggestive of reflux disease, pH testing (with manometry) should be performed in those who are refractory to acid reducing (and/or other) medication, especially if they are under consideration for anti-reflux surgery.

1.7.2 Oesophageal dysmotility

Unlike with GORD, oesophageal motor disorders are varied and treatment options are limited. This is partly because until recently the tools used to investigate them did not provide sufficient insight into the patho-physiological mechanisms behind the various disorders. Furthermore accurate testing prior to and following medical or surgical therapy has been a challenge. Thanks to the advent of recent novel and advanced technology, there has been renewed interest in the study of oesophageal function. Specifically tools such as HRM are routinely being used to study the efficacy of new therapies (medical and otherwise) to treat the many facets of oesophageal dysfunction.

The following review of disease and available therapies mirror the HRM-based classification of dysfunction presented above.

I. OGJ pathology

Hypotensive OGJ pathology is normally linked to GORD. This was discussed detail in section 1.7.1. On the other hand, hypertensive and non-relaxing OGJ disease can contribute to a myriad of symptoms and it can influence motility in the oesophageal body.

A. Achalasia

Achalasia is the most commonly diagnosed primary motility disorder and is second only to GORD as the most common functional oesophageal disease. It has an annual incidence of 0.5-1 per 100 000 with no clear age predilection.[177] Achalasia is characterised by loss of inhibitory enteric neurons. Its aetiology is unknown but one theory is that it is an auto-immune response triggered by a viral infection.[177] Its manometric signature is impaired LOS relaxation and aperistalsis. Typically achalasia presents with symptoms of dysphagia for solids (100%) and for liquids (97%), chest pain (74%) and weight loss (60%).[26] Investigations usually start with endoscopy and/or radiology to rule out anatomical lesions; however endoscopy is only diagnostic in 1/3 of cases and radiology in 2/3.[178] (Figure 1.15)

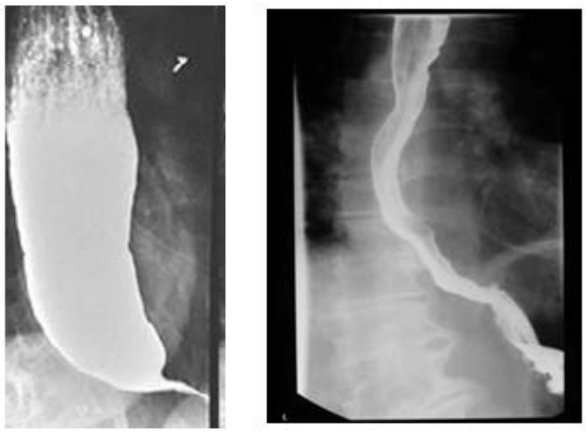


Figure 1.15 Barium swallows of achalasia. The left panel shows typical features (dilated oesophagus with 'bird's beak' OGJ). The right panel is non-diagnostic. This is likely because it is seen early, prior to the oesophageal dilatation stage which follows prolonged outlet obstruction. (see figure 1.13)

With standard manometry, achalasia is diagnostic in 90% of cases, while with HRM using the IRP metric sensitivity and specificity are 98% and 96% respectively.[134] Furthermore, the Chicago group have further subdivided achalasia into 3 subtypes each with its own phenotypic response to therapy.[136] (Figure 1.13 and Table 1.4). Type II, the compression subtype, produced the most favourable outcome to any form of therapy (Botulinum toxin, pneumatic dilatation or Heller myotomy). Type I, classical achalasia, produced a reasonable response to dilatation and myotomy while the spasm subtype exhibited the worst outcome to any form of therapy. When compared to corresponding barium findings, it is theorised that Type II is the prequel to Type I which develops after a prolonged mechanical outlet obstruction. In this regard, it is important to investigate and identify achalasia early to achieve the most optimal response to therapy. It is important to note that Type II and III achalasia can only be diagnosed with HRM.

Achalsia Intervention	Type I Classical	Type II Compression	Type III Spasm	All Types
Botulinum toxin	0% (0/2)	86% (6/7)	22% (2/9	39% (7/18)
Pneumatic dilatation	38% (3/8)	73% 19/26)	0% (0/11)	53% (24/45)
Heler Myotomy	67% (4/6)	100% (13/13)	0% (0/1)	85% (17/20)
All (any) interventions	44% (7/16)	83% (38/46)	9% (2/21)	56% (47/83)

Table 1.4 Response to therapy of achalasia subtypes: Classical, Compression, Spasm (Adapted from Pandolfino et al. Gastroenterology 2008[136])

A Heller myotomy bisects the circular muscles above (usually 4-6cm), through and 1-2 centimetres below the LOS into the gastric cardia. Although a raised LOS pressure is not a necessary diagnostic feature of achalasia, a study of 200 patients who underwent myotomy found that a predictor of post-surgical relief from dysphagia was a pre-operative raised LOS pressure.[179] A 'floppy' (usually anterior Dor) hemi-anti-reflux procedure is commonly performed to prevent post-operative GORD. One study of 43 patients randomised to myotomy with and without Dor fundoplication found that GORD occurred in 48% of those without and 9% of those with a wrap.[180]

B. Structural outflow obstruction

Eosinophilic oesophagitis (EoE) is an allergic immune T-cell–mediated hypersensitivity response leading to eosinophil activation and a fibro-inflammatory reaction.[181] It is characterised by a dense oesophageal eosinophilia (≥15 eos/high power field; HPF) of the oesophageal epithelium with squamous hyperplasia.[182] EoE can result in any combination of oesophageal symptoms; dysphagia, food bolus obstruction, reflux like symptoms or chest pain.[183-185] It can manifest at any age but peaks between ages 20 and 50 years[186] and is more common in males.[187] Endoscopy can be normal although pathognomic features can sometimes be seen; linear furrows, mucosal rings, white exudates and plaques and crepe paper mucosa.[183] Although diagnosis is not aided by pH monitoring,[187] manometry can show features of outflow obstruction with a raised IBP/IRP. (Figure 1.14A, 1.16)

A subgroup of EoE exhibit a response to PPI therapy.[188] Although systemic steroids lead to good histological and symptomatic response,[189] swallowed topical corticosteroids (budesonide or fluticason) is now the main-stay of therapy.[190-192] Other effective, yet less conventional therapies include elimination diets (e.g. six food elimination diet[193]), Leukotriene receptor antagonists (Montelukast)[194] and oesophageal dilatation.[195,196]

Other causes of structural outflow obstruction are a fibrotic stricture at the level of the OGJ due to chronic reflux (Figure 1.17) or a submucosal tumour (Chapter 7 Figure 7.2). Therefore all patients with any form of resistance to flow within the oesophagus or OGJ must have a diagnostic endoscopy and/or endoscopic ultrasound scan.

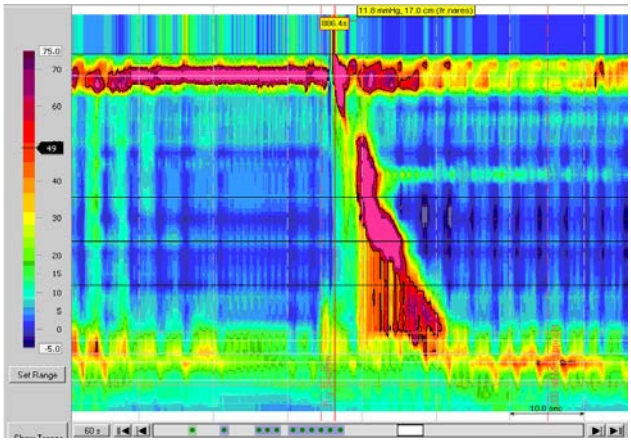


Figure 1.16 Eosinophilic oesophagitis (EoE). HRM of a patient with EoE showing outflow obstruction at the level of the LOS after swallowing bread. This is likely due to fibrosis which can result in late EoE. Interestingly in this case, water swallows resulted in a normal trace.

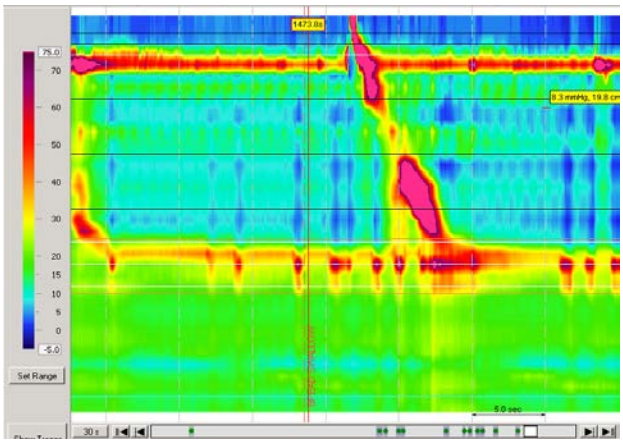


Figure 1.17 Fibrotic stricture. 70 year old female with a long history of recurrent vomiting and chest pain not relieved with lansoprazole. Endoscopy showed Grade C Oesophagitis. 24 hour pH monitoring found evidence of severe GORD with pathology in the upright and supine positions as well as a positive reflux-symptom association for heartburn.

II. Oesophageal body

A. Hypertensive dysmotility

Nutcracker oesophagus is more common in younger patients, while diffuse oesophageal spasm (DOS) is more common in the elderly.[115,197] In those presenting with non-cardiac chest pain, nutcracker oesophagus is the most common oesophageal motor disorder (up to 36%)[198] while DOS is the least (<5%).[199] It is important to note that DOS is not necessarily characterised by high amplitude contractions, rather simultaneous contractility in the smooth muscle oesophagus.[199] Longitudinal studies do not support the concept of progression from nutcracker or DOS to achalasia,[200] and there is no evidence of an inflammatory process or effect on myenteric neurons.[201] On the other hand, there may be an imbalance between the excitatory and inhibitory innervations of the oesophagus as the numbers of choline acetyltransferase-positive myenteric neurones in nutcracker oesophagus are increased.[202] Furthermore, studies have shown that compared to healthy subjects, DOS, nutcracker oesophagus as well as in achalasia exhibit a hypertrophy of the muscularis propria.[203] Therefore these may all be possible targets for therapy.

Currently only 1/3 of patients with hypertensive oesophageal motor disorders find medical therapy to be of benefit,[204] although this is likely due to the paucity of therapies available and their high side effect profile.

Conservative management

Patients are normally initially advised to avoid trigger factors; avoid pro-cholinergic agents (e.g. caffeine), consume soft foods in order to reduce resistance to bolus passage as well as reduce stress and anxiety. In regards to medical therapy, a PPI trial and/or pH study should be considered first as there is a clear (yet unexplained) link between these conditions and GORD.[205-207] If this fails, smooth muscle relaxants are commonly tried. Therapies included under this heading are nitrates, calcium channel blockers, phosphodiesterase type V Inhibitors, oil of peppermint and botulinum toxin injections.

Smooth muscle relaxants

Nitrates have been shown to reduce contraction amplitude and increase the duration of swallow, thus promoting normal peristalsis and reducing symptoms.[208-210] They appear to be most effective in patients with no evidence of GORD.[209] Unfortunately many patients are unable to tolerate nitrates due to the side effects (dizziness and headaches), although patients with good response to short acting preparations seem to do well also on long-acting preparations.[208,209] Calcium channel blockers (Table 1.5) reduce LOS pressure (35%) and peristaltic amplitude (60%) within 20-30 min of oral ingestion, and these effects can last up to 30 min. Nifedipine (20mg) has a greater effect than all other calcium channel blockers and Diltiazem has the least effect on LOS pressure or peristaltic amplitude.[211,212] On the other hand, Richter et al showed that the effect of nifedipine is almost disappeared by 6 weeks.[213] Furthermore, Richter and others have shown that improvement could not be correlated with changes in either LOS or oesophageal amplitude[214] and that there is little or no benefit on *symptom* control.[215,216] As with nitrates, the high side effect profile (hypotension, bradycardia, paedal oedema) reduces long term tolerability.

Agent	n	route	mean pressure pre-	mean pressure post-	
Nifedipine	6	oral	29.0	9.0	Weiser HF et. al. Lancaster: MTP Press Ltd, 1978:565-572.
Nifedipine	6	oral	17.7	7.7	Blackwell JN et al Digestion 1981;21:50-56.
Verapamil	8	iv	20.8	14.1	Becker BS et. al. Am J Gastroenterol 1983;78:773-775.
Nifedipine	10	sl	13.1	9.3	Hongo M et. al. Gastroenterology 1984;86:8-12.
Nifedipine	12	oral	19.1	14.1	Konrad-Dalhoff I et. al. Eur J Clin Pharmacol 1991;41:313-316.
Diltiazem	5	oral	18.4	18.2	Richter JE et. al. Dig Dis Sci 1984;29:649-656.

Table 1.5 Calcium channel blockers. Summary of studies showing the degree of reduction in oesophageal contractility before and after administration of calcium channel blockers in patients with hypertensive oesophageal motor disorders.

Phosphodiesterase V inhibitors (Sildenafil) inhibit the breakdown of nitric oxide in the synaptic cleft. This increase in intracellular nitric oxide induces smooth muscle relaxation. Sildenafil has been shown to improve oesophageal motility in nutcracker oesophagus, hypertensive LOS, focal and diffuse oesophageal spasms by reducing LOS resting pressure, prolonging the duration of LOS relaxation and reducing distal oesophageal contraction amplitude.[217-220] At St Thomas Hospital in London, Sildenafil has been shown to improve symptoms.[221] (Figure 1.18)

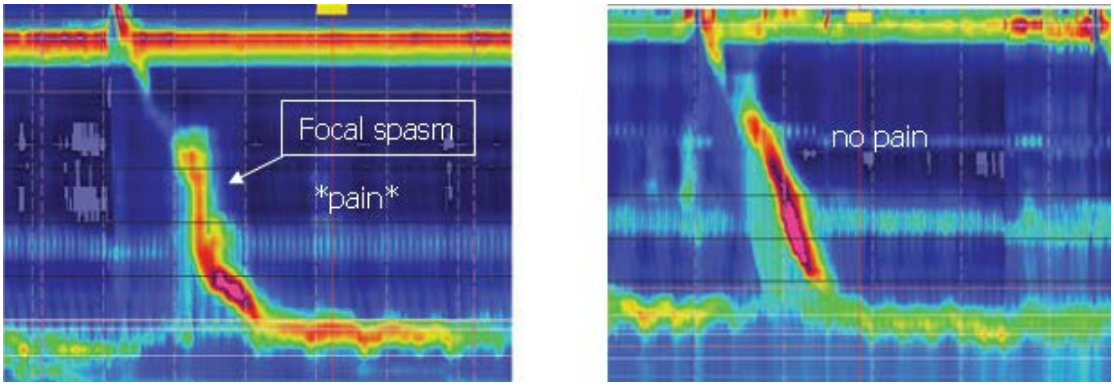


Figure 1.18 Focal spam treated with Sildenafil. 63 year old lady with central chest pain on swallowing. Left panel: baseline HRM trace after swallowing 5 ml of water showing focal mid-oesophageal spasm which reproduced her typical chest pain symptoms. Right panel: 50 minutes after administering 25mg Sildenafil, peristalsis normalized and symptoms disappeared even when she was challenged with solid swallows.
(Reproduced from Fox M, Sweis R et al NGM 2007[221])

Botulinum toxin injected endoscopically into the LOS and/or distal oesophageal body can be used to treat stubborn hypertensive oesophageal motor disorders. This can improve or even relieve symptoms in >50% of patients for up to 1 year.[222,223] A recent randomised controlled study showed that patients presenting with symptoms of dysphagia (rather than chest pain) had the most benefit.[224]

Pain modulators

The benefits of tricyclic anti-depressants, serotonin re-uptake inhibitors and other antidepressants are well established in functional GI disease, including the treatement unexplained non-cardiac chest pain.[91,225-229] Although this group of drugs have no effect on oesophageal function per se, it is theorised that they reduce symptoms due to their effect on visceral sensitivity as they target the central nervous system and sensory afferents. Their influence on anxiety and depression which often co-exist with chronic functional syndromes is also beneficial.

Oesophageal dilatation

Rigid and pneumatic dilation can be used in patients with DOS whose symptoms remain refractory. Although clinical trials are lacking, case series show that at least half have a good outcome although 1:20 have an increased risk of perforation or bleeding.[230-232] At St Thomas' Hospital in 1992, 20 out of 61 patients with DOS had pneumatic dilatations. 14 had a good response, 5 had a poor response and 1 had perforation. Of those with poor response, 3 proceeded to full length myotomy, 2 of whom had relief of symptoms.[230]

Surgery

A small group of patients with severe intractable symptoms might proceed to surgery. A procedure similar in principle to a myotomy for achalasia extends the dissection of the hypertrophied circular muscles as far up as the proximal transition zone. This is often also followed by an anti-reflux procedure to prevent post-operative GORD. Although there are no controlled studies, numerous case series have been reported since the 1960's. Results are less good than for achalasia but recent reports describe good long-term functional outcomes in up to 80% of cases.[233-235]

B. Hypotensive dysmotility

Conservative management

This group of oesophageal motor disorders includes those in whom there is a >3 cm break in contractility as well those with absent peristalsis. Although both are commonly associated with GORD, the latter can include syndromes such as autonomic neuropathy (e.g. diabetes) and connective tissue disorders (e.g. scleroderma). Unfortunately response to medical or surgical therapy is poor and conservative management is often the best that can be offered. Commonly patients are advised to eat upright, chew thoroughly, use liquids liberally (especially carbonated drinks) and avoid 'difficult' food items such as steak and dry bread.

GORD therapy

Dysphagia is present in 20-50% of patients referred for anti-reflux surgery, many of whom have hypotensive dysmotility.[176,236,237] In one study of 163 GORD patients about to undergo anti-reflux surgery, dysphagia was relieved in all but 5 of the 60 who had pre-operative dysphagia.[176] However, prior to embarking on surgery, an empirical trial with optimal doses of acid reducing medication should be considered with pH testing in those who do not respond (treat and test policy; Section 1.7.1).

Contractility stimulants

It is theorised that patients with hypotensive dysmotility have an increased activity of nitric oxide synthase within the smooth muscle, possibly with muscle fibre loss (myopathy) and replacement with fibrous tissue.[202] These may be useful targets for therapy although in the case of muscle fibre loss stimulation mechanisms are unlikely to be effective.

Domperidone (dopamine agonsit) is a common drug prescribed in the outpatient setting to treat perceived reduced gut motility disorders. Very few studies have assessed oesophageal emptying of solids following domperidone. A study of 12 patients with diabetes mellitus and autonomic neuropathy showed that Domperidone did not increase solid oesophageal emptying compared to controls.[238]

Erythromycin, a motilin agonist, is another prokinetic often prescribed. In a study of 45 patients with diabetes mellitus, Chang et al showed that the mean transit time of a radionucleotide liquid and solid meals dropped from 9.32±1.12 to 6.28±0.91 s ($p<0.05$) after receiving a 2 week course of erythromycin.[239] Chrysos et al showed that in patients with GORD, iv erythromycin improved oesophageal peristalsis and function by increasing LOS pressures as well as contractility and duration of swallows.[240]

Bethanechol (Urocholine) is a direct-acting muscarinic receptor agonist which enhances the effect of acetylcholine directly at the postganglionic cholinergic receptors. It has been shown to increase LOS pressure and improve oesophageal contractility in healthy subjects.[241] More recently in a study of 7 patients with hypomotility, Agrawal et al showed that bethanechol significantly increased distal

oesophageal contractions and bolus transit times for both liquid and solid swallows up to 40 minutes after ingestion.[242]

A break of >3 cm in the 30 mmHg isobaric contour defines hypotensive dysmotility.[131] It is not uncommon for such a break to occur in the proximal oesophagus. If consistent at the PTZ (Figure 1.11) this can lead to bolus escape and in turn symptoms (dysphagia, chest pain). In 2007 Fox et al showed that a 7 day course of Tegaserod, a partial 5-hydroxytryptamine 4 receptor agonist with prokinetic effects on the gastrointestinal tract, promoted mid-oesophageal contractility and shortened the proximal break in contractility thereby improving coordination and symptoms. With synchronous manometry and video-fluoroscopy, a radio-labelled bolus which had remained in stasis within the PTZ at baseline was seen to progress after therapy with ease.[36] Unfortunately, in 2007 the USA Food and Drug Administration withdrew Tegaserod after concerns that it may increase the risk of heat attach and stroke. This decision was based on 13 cardiovascular events out of 11,614 who were taking the drug. Tegaserod can still be obtained on a named patient basis.

1.8 Aims and objectives

With the advent of new technology (e.g. Bravo and HRM) there has been a resurgence of interest in the study of oesophageal function and disease. This technology provides a better understanding of the dynamic function and structure of the oesophagus and LOS. It also offers the opportunity to test the efficacy of new drugs and surgical techniques which was previously a challenge or even impossible. On the other hand, such sensitive techniques run the risk of reducing specificity as normal function can be perceived as being pathological. In order to differentiate these and to improve outcome, therapy needs to be directed at symptom-inducing dysfunction. (Figure 1.19) It would be wrong to proceed to anti-reflux surgery in a patient with borderline pH measurements based on only one 24 hour pH study. Similarly to initiate medical or surgical therapy based on a few aberrant water swallows using manometry is unsafe. Ultimately the diagnosis reached is only as good as the tools and methodology used to define it.

The purpose of studies in this thesis is to optimise the utility of advanced technology in oesophageal physiology by reproducing normal behaviour during pH and manometry testing. Advances in oesophageal physiology that will be explored in this thesis are:

1. Prolonged wireless pH monitoring
2. High Resolution Manometry while eating and drinking.

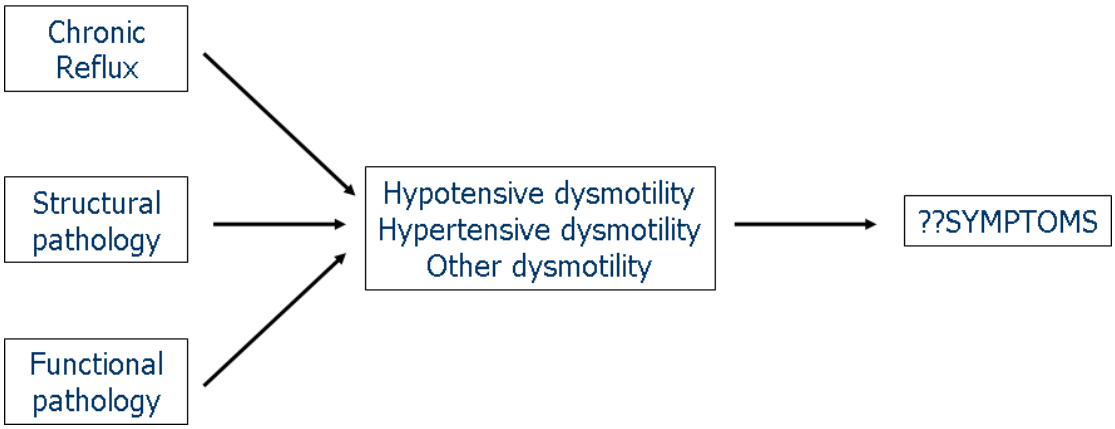


Figure 1.19 Therapeutic algorithm; therapy should target dysmotility associated with symptoms rather than any dysmotility event that may arise.

Bravo; Wireless pH monitoring

NICE guidelines suggest that wireless pH monitoring should be reserved only for those who are intolerant of the nasal catheter.[109] Wireless pH monitoring is available at only a few tertiary referral centres mostly for patients who are intolerant the nasal catheter. It is also increasingly used to study those with negative catheter-based pH studies yet ongoing typical symptoms.

The aims of studies using Bravo in this thesis will be:

1) To examine the tolerability and diagnostic yield of prolonged (48 hour) wireless pH monitoring in patients who failed standard (24 hour) nasal pH-studies.
2) To investigate whether prolonged (up to 96 hour) wireless pH monitoring improves the diagnosis in patients with ongoing symptoms suggestive of GORD but with negative standard (24 hour) catheter-based pH results.

High Resolution Manometry

With HRM although more physiological testing can be performed, this has not yet entered routine clinical practice. To induce relevant symptoms by reproducing normal eating and drinking is a novel concept which has not yet been assessed nor standardised.

The aims of studies using HRM in this thesis are:

1. To assess the effects of changing body position, bolus consistency and bolus volume (physiological challenge swallows) on oesophageal function in healthy volunteers and in turn to produce normative values.
2. To assess the inter-observer agreement for 'physiological challenge' swallows in health.
3. To assess the efficacy of novel methodologies, metrics and normative values acquired in health on the diagnostic yield and post-therapy outcome of patients presenting with typical oesophageal symptoms (reflux and dysphagia).

Chapter 2

Methods and analysis

2.0 Introduction

The methodologies described in this chapter are universal to all studies performed in this thesis. Variations or additions for individual experiments will be described in the corresponding chapters. Routinely patients will have had manometry performed in advance of the pH studies; however to follow the sequence of studies presented in this thesis, methodology for ambulatory pH testing will be presented first.

Patients included in this thesis were recruited from the same pool of patients referred to the Oesophageal lab for the investigation of heartburn, regurgitation, chest pain and dysphagia as the primary presenting complaint. Referrals were received from within the hospital, the London area, Kent and sometimes beyond as the Oesophageal lab at St Thomas' hospital is considered to be a tertiary referral centre of excellence.

Methodology for the insertion and analysis of catheter-based and wireless pH monitoring[83,85,103] as well as for the high resolution manometry[36,125,243] are standardised and clearly described in the literature. The introduction of 'physiological challenge swallows' has also been explored in various formats using and technologies[36,137,244,245] but have never been performed using the methodology and analysis techniques presented in this thesis. The intent was to replicate normal facets of behaviour while at the same time reproducing earlier 'non-physiological' studies for comparison.[121,130,246,247]

2.1 Catheter-based pH Studies

(Appendix 1 and 2)

Patients with typical reflux symptoms of heartburn, regurgitation and chest pain were recruited from the routine referral pool. A thin (3mm) pliable catheter with at least one antimony pH sensor (Slimline™, Medtronic, Inc., Shoreview, MN) was calibrated at 25°C in pH 7.01 and pH 1.07 buffer solutions as per the manufacturer's protocol (Medtronic Inc., Shoreview, MN). The LCD screen on the recorder provides a continuous pH reading to aid this process.

After numbing the nares and pharynx with up to 10 ml of Xylocaine spray (effects of which lasts no more than 10-20 minutes), the catheter was passed trans-nasally through the oesophagus while asking the patient to sip water through a straw to aid its passage. Gastric acid was detected on the receiver screen once the sensor reached the stomach. At this point the catheter was drawn back into the oesophagus and positioned so that (by convention) the pH sensor lies 5 cm proximal to the superior aspect of the manometrically determined LOS. The catheter was then connected to the portable digital data recorder (Digitrapper pH400, Medtronic, Inc., Shoreview, MN), and secured to the side of the face and neck with tegaderm. (Figure 2.1) The recorder could then be carried in a holster or clipped onto a belt to permit freedom of movement.

Figure 2.1 Catheter-based pH monitoring. Typical placement and position of the nasal catheter for ambulatory pH monitoring and manometry.

Patients were always provided with a diary to record symptoms, meal/snack start and finish times, changes in position (upright and supine) and the occurrence of symptoms. (Appendix 2) Although these events could also be recorded directly onto the digital device with up to 3 buttons pre-assigned to the patient's unique symptom combination (e.g. heartburn, regurgitation, chest pain), a dual record of events (paper and electronic) was always used to minimise the risk of human error. Patients were recommended to pursue their normal daily activities and diet. In order to eliminate swallow-associated pH artefacts, patients were instructed not ingest acid-based foods and fluids such as fruits, citrus products, fruity and carbonated drinks or alcohol. Tea and coffee were only permitted if milk was added.

Patients were required to return after 24 hours for catheter removal. Information collected from the device was then downloaded onto the proprietary software (Polygram net) in preparation for analysis. A new catheter was used for every patient.

Dual channel catheters with an additional pH sensor located 15cm proximal to the LOS were sometimes used if patients had proximal or atypical symptoms (e.g. laryngo-pharyngeal reflux or cough). Although patients with atypical symptoms were not excluded, typical symptoms of reflux (heartburn, regurgitation or chest pain) were required to be the primary presenting complaint to fulfil inclusion criteria for studies in this thesis. For the purpose of studies in this thesis, only data from the sensor at 5cm proximal to the LOS was analysed**.**

2.2 Wireless pH Monitoring (Bravo®)

(Appendix 3 and 4)

All patients recruited for Bravo studies presented in this thesis were selected from the same pool of those referred to the St Thomas' Oesophageal lab with typical symptoms of reflux (heartburn, regurgitation, chest pain with/without dysphagia). The selection process for Bravo patient recruitment adhered to guidelines set forth by NICE.[102] Apart from intolerance to the catheter or re-referral for ongoing symptoms following negative catheter-based studies, there was no bias in the selection of patients for Bravo compared to the catheter-based studies.

2.2.1 Bravo calibration

The Bravo capsule is oblong in shape; dimensions of 6.0 x 5.5 x 25 mm. It consists of an antimony pH electrode and reference electrode located on the distal tip as well as an internal battery and transmitter contained within the epoxy-coated capsule. (Figure 1.5 and 2.2). The pH capsule sends a signal to the receiver through a radio frequency signal which is in the unregulated 433 MHZ band.

The capsule was prepared in the oesophageal lab several hours prior to endoscopy. This 15-20 min procedure was routinely performed by the Oesophageal lab technicians. In accordance with the manufacturer's protocol (Medtronic Inc., Shoreview, MN), the capsule was first activated by a magnetic switch and soaked in a

pH 7.01 solution for 10 minutes before being placed into a pH 1.07 buffer solution at 25°C to complete the calibration process. The capsule and receiver were checked to confirm accurate signal capture and transmission of data.

2.2.2 Bravo capsule insertion

After an overnight fast all subjects were first required to visit the oesophageal lab where a detailed discussion regarding the Bravo technique and risks associated took place. Also instruction regarding diary card recording and Bravo operating instruction was provided. The patient was then sent to the endoscopy unit where the procedure was discussed again including the endoscopy technique and all questions were answered prior to being asked to sign the consent form for the procedure.

Gastroscopy was performed in the left lateral decubitus position, usually under conscious sedation. Mean doses for sedation (midazolam 7mg (0-10mg) and fentanyl 67 mcg (0-150)) were somewhat higher than for diagnostic gastroscopy (midazolam 4mg (0-5mg)) because the majority of these patients were sensitive to oro-pharyngeal manipulation (most having been intolerant to the nasal catheter) and because the procedure required several consecutive intubations.

A complete gastroscopy to the second part of the duodenum was always initially performed and any pathology including oesophagitis, Barrett's oesophagus and hiatus hernia were identified and their margins measured relative to the incisor teeth. Oesophagitis and Barrett's oesophagus were classified according to agreed criteria; Los Angeles Classification[248] and Prague classification respectively.[249] (Appendix 5 and 6) After the position of the squamo-columnar junction (SCJ) was confirmed, the gastroscope was removed and the Bravo delivery device was passed orally. (Figure 2.2) The gastroscope was then re-inserted to confirm passage of the delivery device into the oesophagus (and not the trachea) before it was again withdrawn. The delivery device was then positioned such that the capsule was 6 cm proximal to the SCJ; the high pressure zone is 1-1.5cm proximal to the SCJ which is equidistant to the conventional pH catheter sensor target position of 5 cm proximal to the LOS.[103] As the SCJ is not easily identifiable in circumferential Barrett's oesophagus, the position

at which the gastric rugae ended and oesophageal mucosa began was used as an alternative landmark.

When in position, an external vacuum pump was activated in order to apply suction to the pH capsule ‘well’, a 4 mm in diameter and 3.5 mm deep depression in the proximal part of the capsule (Figure 1.5). To confirm good apposition and retention of the adjacent mucosa within the well, the investigator ensured that the vacuum pump was stabilised at >510 mmHg for up to 60 seconds. This was always confirmed and timed by an endoscopy nurse assistant. A plastic safety guard on the handle of the delivery system was then removed and the activation button on the handle was depressed with the thumb (Figure 2.2A). This manoeuvre triggered a spring-loaded, stainless steel pin to be driven across the capsule well and through the retained mucosa, thus securing the capsule to the mucosal wall. The activation button was then twisted clockwise 1/8 of a turn and re-extended to release the capsule from the system. After withdrawal of the delivery device, capsule attachment and accuracy of positioning was always confirmed under direct vision with a final gastroscopy. A picture was always taken for the record. (Figure 2.2C) The receiver was then activated, and when confirmed on the LCD screen to be transmitting successfully recording would commence.

The steps described were replicated for every patient included in Bravo studies of Chapters 3 and 4.

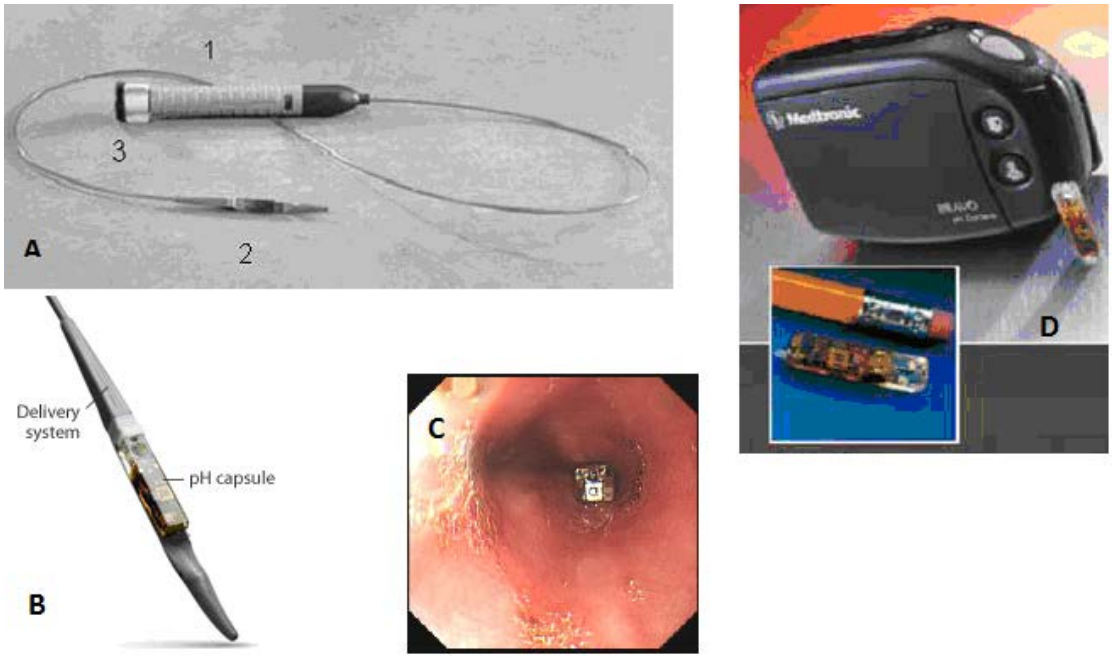


Figure 2.2 Bravo delivery system, capsule and receiver comes as a pre-packaged assembly. The handle of the delivery system is separated from the housing of the capsule by an 80 cm 6 F long tube with markings on the side. (A1-3 and B). The delivery device (A and B) is normally inserted orally down the un-anaesthetised pharynx of a (normally) sedated patient. Markings on the side (A3) depict the distance from the incisors. The capsule is deployed 6 cm above the anatomical z-line (or 5 cm proximal to the proximal LOS high pressure zone) (C). The delivery system is then withdrawn and the receiver is synchronized. (D) It remains attached to the patient (via belt clip or shoulder pouch) for the duration of the study. Capsules fall off spontaneously (median 5 days).[103] Complications requiring its early removal are rare in the literature and have never been required in its 9 years of use at St Thomas' Hospital.
(Images reproduced from various websites including Given Imaging. The endoscopy image (C) was from a patient in the study described in Chapter 4)

Unlike with the catheter-based studies, Xylocaine was not used to anaesthetize the pharynx during insertion. Experience at St Thomas' Hospital have shown that in cases of primary non-adherence, the capsule preferentially tended to migrate upwards; a capsule entering the anesthetised pharynx runs the risk of being aspirated. Such an adverse event has not occurred in any patient included in this thesis, nor indeed in any patient who has had a Bravo procedure at St Thomas' Hospital thus far.

Patients were requested to return after 48 hours. At this (2nd) visit data from the receiver was downloaded (Polygram net, Medtronic) and the capsule transmission checked by the lab technicians. 48 hours is currently the standard Bravo measuring time set by the proprietary software and is what is most commonly quoted in the literature.[103,250] For the Bravo study presented in Chapter 3, analysis ended at 48 hours as per the standard. For the Bravo study presented in Chapter 4, if the capsule remained in situ and a good signal persisted, batteries were changed and the study was extended for a second 48 hours, thus providing a maximum recording time of 96 hours.

The Bravo capsule is known to remain in situ for a median of 5-6 days,[103] and experience from the St Thomas' Oesophageal lab is that 69% of capsules remain in place by day 4 with a 10% drop off rate every 24 hours from day 2 (Figure 2.3; unpublished data). Once the capsule drops, it is passed per rectum and is rarely noticed by the patient.

The same advice to avoid acidic food and drink was given as for catheter-based studies in order to avoid swallow-associated acid artefacts as the catheter cannot differentiate between acid which is refluxed or swallowed. Otherwise patients were encouraged to undertake their 'normal' daily activities and diet. A similar diary card was provided and patients were advised to record all their activities and food/fluid consumption in detail.

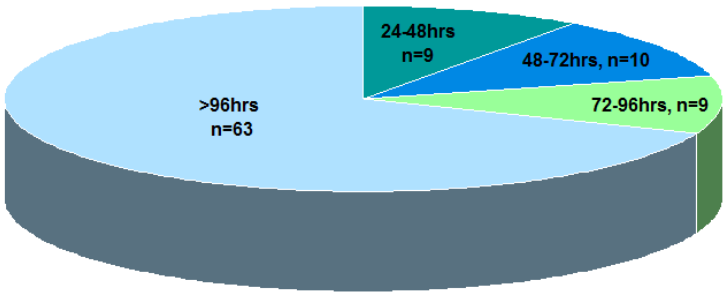


Figure 2.3 Capsule drop offs out of 91 consecutive patients between 2009-2010 at St Thomas' Hospital Oesophageal lab showing 10% drop off per 24 hours from day 2.

2.3 pH monitoring analysis

2.3.1 Oesophageal acid exposure

Ambulatory pH monitoring provides an assessment of frequency and duration of reflux events as well as the degree of association between these events and symptoms. Standard analysis of reflux events undertaken in these studies included a measure of:

- total number of reflux episodes
- total acid reflux (TR) - the percentage of time that the pH drops below a certain value (by convention pH of 4) over 24 hours. TR has been shown to be the single most robust and reproducible diagnostic marker of GORD.[251]
- upright and supine reflux – subdivisions of the TR

Cut-off values

According to the BSG Clinical practice guidelines a total percent time that pH drops below 4 (TR) of <5% is accepted as normal in the absence of locally determined ranges for defining the limits of physiological acid reflux.[78] However a cut-off value of 4.2% is the most common published TR value quoted for catheter-based studies[85,250] and 5.3% for wireless studies.[103] The difference is not only because the wireless pH study is more prolonged (and thus likely to pick up more reflux events) but also because of the less restrictive effects on diet and physical activity which increases the frequency of reflux-provoking activities. In order to compare results with the current literature, for categorical analysis (i) a standard cut-off value of 4.2% for both procedures and (ii) a specific cut-off values of >4.2% for 24 hour catheter-based studies and >5.3% for prolonged wireless studies were presented for all pH data in this thesis.[103] For upright and supine acid reflux measurements¸ accepted normal values for the total percent time pH drops below 4 are <8.15% for upright reflux and <3.45% for supine reflux. At present, the literature does not differentiate cut-off values for upright and supine reflux between 24 hour catheter-based and prolonged wireless pH monitoring.[78]

Worst day vs. Average analysis

For prolonged studies data published in the literature usually quote the ‘Single worst day’ results. Alternatively the ‘Average’ of all days recorded could be used.[85,103,250] It

is not yet clear which is more clinically relevant. Therefore studies in this thesis are presented using both 'Worst day' and 'Average' analysis for measurements of i) oesophageal acid exposure and ii) reflux-symptom association. These concepts will be explored in the corresponding chapters.

DeMeester score

As there is a wide day-to-day variability of oesophageal acid exposure for every individual,[83-85] recorded variables are referenced to known control values. One such system is the revised Johnson-DeMeester (DM) score. This is a clinically validated system for assessing the severity of reflux disease. A composite score is calculated based on the number of reflux episodes and duration of acid exposure in the upright and supine positions (weighted towards the percentage time of supine oesophageal pH exposure).[252] The agreed upper limit of normal for the DM score is 14.72. However, DM is validated only for 24 hour studies using the catheter-based system. As the purpose of these studies is to compare catheter-based studies with prolonged (≥48 hour) wireless pH monitoring, DM was not presented.

2.3.2 Measurements of symptom association

To define the temporal relationship between reflux and symptoms, three symptom-association analyses have been described for clinical reporting and research.[76] These are routinely incorporated into commercial ambulatory pH proprietary software. By convention, an association is assumed if a reflux event precedes a symptom event within a two minute time window.

1. Symptom Index (SI)[253]

The proportion of patient symptoms that are related to reflux

$$\frac{\text{Number of reflux related symptom episodes}}{\text{Total number of symptom episodes}} \times 100$$

A symptom association of ≥50% is considered to be positive (pathological).

This is a common and simple tool and is automatically calculated by the dedicated proprietary software. This parameter has been shown to be a good predictor of response to therapy; patients with typical symptoms and evidence of oesophageal acid exposure with a positive SI have the best response to acid reducing medication.[75] Furthermore SI has been shown to be clinically useful in the assessment of visceral sensitivity.[151] This was the primary symptom association parameter used in studies presented in this thesis.

2. Symptom Sensitivity Index (SSI)[254]

$$\frac{\text{Number of reflux related symptom episodes}}{\text{Total number of reflux episodes}} \times 100$$

SSI of ≥ 10% is considered to be positive (pathological).

SSI does not take into account the total number of symptom episodes. This assessment is quoted with reducing frequency in the literature and has been shown at St Thomas' Oesophageal lab to have a very weak correlation with reflux acidity and likelihood of triggering symptoms (unpublished). Therefore it was not included in studies presented in this thesis.

3. Symptom Association Probability (SAP)[255]

SAP is performed by dividing the 24 hour period into 2 minute segments and determining whether (or not) a symptom occurred 2 minutes prior to every episode of

reflux recorded. It uses a 2x2 contingency table (fisher exact test) to calculate the probability that the relationship observed between symptoms and reflux is not brought on by chance. The p value is then subtracted from 1 and multiplied by 100 to provide an SAP value as a %. So a p value of 0.05 is equivalent to an SAP of 95% (1-0.05=0.95 x 100). By statistical convention an SAP of ≥ 95% is considered positive (pathological). Independently SAP has been shown to be a good predictor of the success of anti-reflux surgery.[256] This parameter was used in addition to SI in Chapter 4 and was calculated manually to accommodate for the prolonged studies of wireless pH monitoring (see below)

Standard analysis and report

A typical Bravo report is shown in figure 2.4 and 2.5; a plot of the entire 48 hour study period is presented. By convention, a drop in the pH below 4 points to an acid reflux episode. The plot could be 'zoomed in' for closer scrutiny of any interval or length of time. This facility was useful whenever confirmation of automated analysis was required. Information completed in the diary card was entered into the computer manually. These included meals (as well as snacks and drinks) and periods when the patient was supine. Episodes that should be ignored and not analysed (e.g. if acid containing foods/drinks were consumed or periods where the signal was lost) were also registered. This exercise was performed routinely by either the researcher or the Oesophageal Lab technicians for all patients. Once all data entry and final amendments were completed, the software automatically analysed the study and produced a report which highlighted all essential landmarks: symptom events (red and pink lines), supine periods (green blocks), meal times (yellow bars) and periods to be ignored (purple). Data from the automated analysis was then interpreted clinically and a standard report was generated for every patient and delivered to the referrer. Therapeutic decisions were made by the referrer and not by the researcher.

Further analysis related to the studies in Chapter 3 and 4

Results for every 24 hour period (oesophageal acid exposure, SI and SAP) were presented as a separate set of tables. This was followed by a combined average measure of the entire study period. Figure 2.4 and 2.5 portray the first 24 hour Bravo

result of a typical patient as it would appear in a standard report. Definition of terminology in the report:

- 'Duration of period' for reflux events - the total study time minus the periods to be ignored. This was then further subdivided into the time spent in the upright and supine positions. Unless specifically indicated prior to analysis, meal times were not automatically 'ignored' in these studies. Therefore careful and detailed instruction to avoid acidic foods/fluids was essential to avoid acid reflux artefact.
- 'Duration of period' for symptom events - the software considered each symptom to comprise of a 2 minute interval. This 2 minute time window is required to detect an association with the preceding reflux event. Therefore, heartburn 'duration period' of 4 minutes implies 2 heartburn episodes and a regurgitation 'duration period' of 6 minutes implies 3 regurgitation episodes within the 24 hour time period.
- 'Number of Refluxes' for reflux events - the number of reflux episodes subdivided into 'Total', 'Upright' and 'Supine'.
- 'Number of Refluxes' for symptom events – the values that appear beneath the Symptoms columns indicate the number of reflux-related symptom episodes which preceded every symptom (by up to 2 minutes). This value was important in calculating the symptom index (see next).
- 'Fraction time pH<4 (%)' - the total percent time that the pH dropped below 4. Presented for 'Total' (TR), 'Upright' and 'Supine' periods.

Although normally automated, SI and SAP could also be manually calculated; this was the standard for the prolonged studies presented in Chapter 4:

1) **SI (Symptom Index)**

   As described above, SI is the total number of symptom-related reflux episodes ÷ total number of symptoms x 100. An example, of the first 24 hours is presented in Figure 2.5; the total number of reflux-related regurgitation episodes was 1, and the total number of symptoms was 3 (6 minutes ÷ 2 = 3), therefore the SI would be 1 ÷ 3 x 100 = 33.3%.

2) **SAP (Symptom Association Probability)**

   SAP is more complex. An assessment was made of how many reflux events and symptom events occurred separately, together or not at all. A fisher exact

test (2 x 2 table) was then annually created to fit this information and the SAP was calculated from the p value of the fisher exact test.

Fisher exact test 2 x 2 table:

R+S+	R-S+
R+S-	R-S-

R + Reflux events

R- No reflux events

S+ Symptom events

S- No Symptom events

An example of a manual SAP calculation using the fisher exact test for a patient used in the study presented in Chapter 4 using the information from Figure 2.5; within a 24 hour period the patient had 3 regurgitation symptom events and 64 reflux events but only 1 of these was associated with reflux. Therefore R+S+ was 1, R+S- was 64 – 1 = 63 and R-S+ was 3 – 1 = 2. To calculate R-S-, first the 24 hour period (24 hrs x 60 min = 1440 min) was divided into 2 minute intervals (1440 min ÷ 2 = 720). This value was then subtracted from the total number of '2 minute intervals' during which regurgitation or reflux events did occur: 720 – (64 + 3) = 653. The fisher exact test 2 x 2 table would then appear as follows:

1	2
63	653

This produced a p value of 0.2443. Therefore, 1 – 0.2443 = 0.7557 which was then converted to a percentage (0.7557 x 100 = 75.6%). Therefore the SAP was 75.6%. A significant p value was considered to be <0.05 which is equivalent to an SAP of >95%. Therefore in this case, as the SAP was <95%, the result was non-significant and negative.

Another example (not presented in the figures) was a patient with 101 reflux events and 9 heartburn symptom events within a 24 hour period. If 6 of these were associated, the fisher exact test 2 x 2 table would appear as follows:

6	**3**
95	**610**

This produced a p value of 0.0004 which gives a positive SAP of 99.96%, a significant and positive result.

When performed manually, the parameters for reflux and symptom association can be re-calculated and extended to any length of time. The proprietary software already provides an average for the 1st 48 hours (Chapter 3), but the results need to be performed manually to include 3 and 4 day studies (Chapter 4). Furthermore, to optimise the reflux-symptom association in patients with very few symptoms, studies in Chapter 4 combined all symptom events to produce an overall reflux-symptom association value for *any* symptom. Both individual as well combined symptom data were presented in Chapter 4.

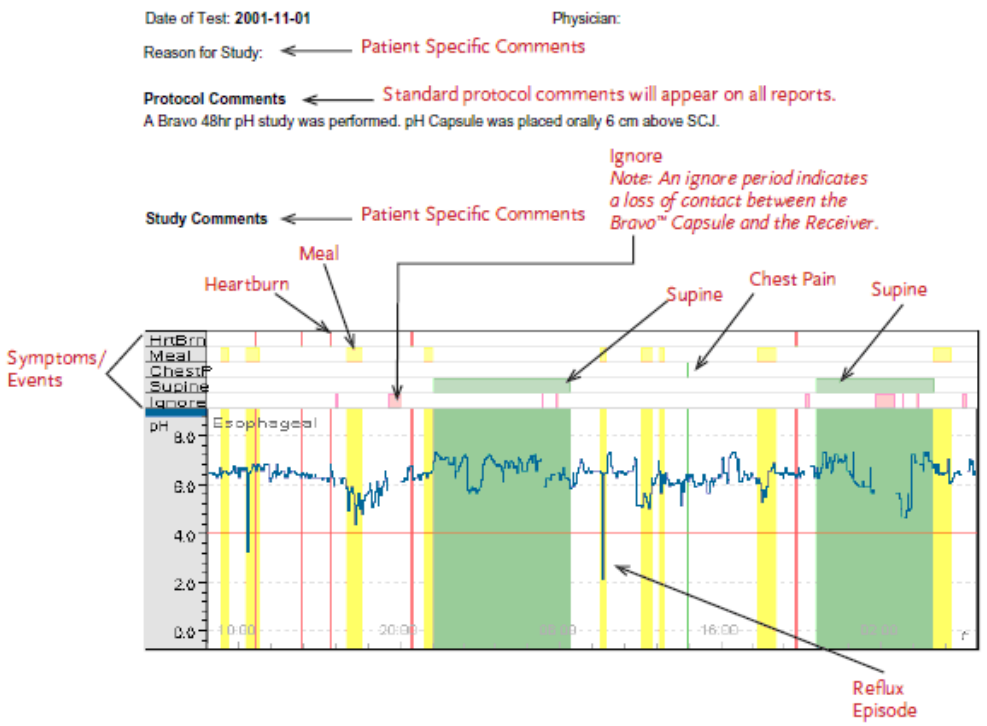


Figure 2.4 Typical 48hr pH trace for wireless pH monitoring. Detail of the plot is presented in the text. (Reproduced from Polygram net user information documents.)

Reflux Table - Day1

	Total	Upright	Supine	Meal	PostPr	HrtBrn	Regurg	ChestP
Duration of Period (d,hh: mm)	23:56	16:28	07:28	01:01	02:00	00:04	00:06	00:02
Number of Refluxes	64	27	37	0	9	0	1	0
Number of Long Refluxes>5 (min)	3	0	3	0	0	0	0	0
Duration of longest reflux (min)	20	4	20	0	3	0	0	0
Time pH <4 (min)	73	20	53	0	5	0	0	0
Fraction Time pH <4 (%)	5.1	2.1	11.8	0.0	4.2	0.0	5.0	0.0

SAP Table - Day1

	Total
HrtBrn	26.8
Regurg	**75.6**
ChestP	18.8
Cough	0.0
Belch	0.0
Other	0.0
vomit	0.0

SI Table - Day1

	Total
HrtBrn	0.0
Regurg	**33.3**
ChestP	0.0
Cough	n/a
Belch	n/a
Other	n/a
vomit	n/a

DeMeester Score-Day1

Total score = 26.8 , DeMeester normals less than 14.72 (95th percentile)

Figure 2.5 Bravo software results table. A sample table of a patient from Chapter 4 showing a summary of the data calculated by the software in the first 24 hours.

2.4 High Resolution Manometry (HRM)

All healthy volunteers recruited for HRM studies in Chapter 5 were friends, family and colleagues of the investigator as well as junior doctors and fellows rotating through the Oesophageal lab and the St Thomas' gastroenterology department. For the study in Chapter 6, consecutive consenting patients were recruited between December 2008 and September 2009. Patients were selected from the same pool of those referred to the St Thomas' Oesophageal lab with symptoms of heartburn, regurgitation, chest pain and dysphagia.

The 36 sensor solid state HRM catheter (used for all studies in this thesis) is 4.2 mm in diameter and consisted of circumferential pressure sensors 2.5 mm in length arranged at 10 mm intervals (ManoScan 360, Sierra Scientific Instruments, Mountain View, CA). This is covered by a silicone-based thermal plastic elastomer. Each sensor detects pressure from 12 separate loci around its circumference. (Figure 2.6) Using pressure transduction technology pressures from each locus is averaged. Computer processing then collects information from all pressure sensing elements to produce circumferential pressure measurements incorporating the entire catheter length which would then be displayed as a spatio-temporal plot captured in real time. (Figure 1.7)

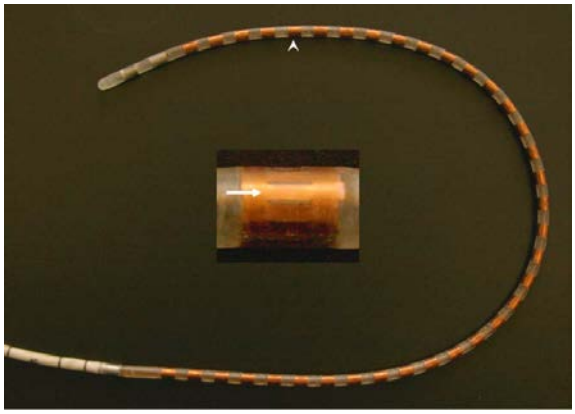


Figure 2.6 HRM sensors. Sensors are copper coloured cylinders (white *vertical* arrow) which are spaced at 10mm intervals. Pressure is detected from 12 loci around each cylinder circumference (1 locus = white *horizontal* arrow from the magnified sensor in the centre).
(Reproduced from Colour Atlas of High Resolution Manometry, Jeff Conklin et al 2009)

2.4.1 Decontamination and sheathing of the HRM catheter

The HRM catheters are re-usable (up to 200 times) although their life-span can be extended (400 times or longer) with ongoing service. Therefore it is essential to maintain optimal disinfection without causing damage to the sensitive silicone coating or sensors. This was achieved by (I) disinfecting and (II) sheathing the catheter. The catheter was stored in its designated box after cleaning and in between uses for all patients. This technique was performed routinely by the investigator prior to and after every patient.

I) Disinfection

Disinfection was always performed with gloved hands and an apron in the Oesophageal Lab clinical room. The Tristel chemical biocidal wipe system was used to disinfect catheters prior to and after every use. (Figure 2.7) Tristel's patented disinfectant incorporates three individually packaged sachets (wet wipes) and a foam pump. Decontamination was a 3-step process during which the length of the catheter would be carefully wiped in a unidirectional (proximal to distal) fashion with gloves changed prior to every step:

1) Pre-clean wipe - composed of a 'low-foaming surfactant system' combined with 'triple enzymes' which produce an ultra-low surface tension suitable for cleaning of any hard surface. This removed organic matter which may have deposited on the catheter surface.

2) Sporicidal, mycobactericidal, bactericidal, virucidal and fungicidal foam pump was directly applied to the second wipe to activate the disinfectant. This could kill almost any organism within 30 seconds of contact.

3) Rinse wipe - this final wipe was impregnated with 'de-ionised water' and a 'low-level of antioxidant' which removed and neutralized any chemical residue that remained.

Figure 2.7 Tristel wipe disinfecting instructions.

(Taken from the Tristel fact sheet.)

II) Sheathing

Manoshield™ (Sierra Scientific Instruments), a sanitary catheter sheath, was applied over the HRM catheter to minimise wear and tear and to act as a physical barrier between the patient and catheter. (Figure 2.8) A sheath was utilised for every subject who underwent HRM.

Figure 2.8 HRM catheter sheath. After completion of the Tristel biocidal three step wipe, the catheter was covered with a thin layer of talk (left panel). Then the thin, hypo-allergenic Manoshield sheath was slid over the catheter (similar to a condom; middle panel). Once inserted to a designated pre-marked position at the tip, a foam 'slider' was passed over the sheath to ensure all air residue was expelled (right panel). The slider was then secured at the hilt with an elastic band and the catheter was ready for use. If during calibration it was noted that some air residue remained within the sheath, the foam 'slider' could again be brought down to the tip, pulled back and secured at the original proximal position.

2.4.2 Calibration

After entering patient details, the prepared catheter was connected to the Manoscan system. The sheathed portion of the catheter was then inserted into the calibration chamber and sealed proximally. Sensors were then interrogated as the machine sequentially increased the compartmental pressure within the chamber up to 300mmHg before dropping back to atmospheric pressure. The response characteristics of each sensing element ideally should be accurate to within 1 mmHg. Defective sensors were highlighted by the software and these were then masked manually. For studies in this thesis, catheters with >3 defective sensors were replaced.

2.4.3 Catheter insertion

(Appendix 1 and 8)

Patients were required to be alert and un-sedated for the procedure. Only Xylocaine 1% was used to locally anaesthetize the nostril (2-3 sprays) and pharynx (5-6 sprays). The catheter was then inserted through either nostril and down the oesophagus while the patient sipped water through a straw in a similar manner to the pH catheter insertion technique. The oesophageal anatomical landmarks could be clearly visualised on the monitor as the catheter progressed down the oesophagus. Insertion was terminated as the catheter crossed the OGJ and entered the stomach. It was then withdrawn such that the Manoscan image included the entire oesophagus from the pharynx to at least 3 cm into the gastric cardia. The position of the LOS was confirmed by deep inspiration to highlight the diaphragm pressure inversion point (pinch). Once finalised, the catheter was taped to the side of the face and neck as it curled behind the ear to reduce catheter movement and pharyngeal irritation. (Figure 2.1) Position from the nares was then recorded as a reference for automated calculations.

2.4.4 HRM study

All studies presented in this thesis were performed by the investigator. Tests were performed in the physiological upright seated position, an important variation to the original validation studies which were performed in the supine position.[121,130,246,247] In healthy subjects, water and bread swallows were then repeated in the supine position (see later). Prior to initiation, study participants were instructed to inform the investigator of any symptoms they were to experience as soon as they occurred so that they could be marked directly onto the HRM trace. Subjects were never 'prompted' for symptoms during the analysis. Symptoms described during the study included pain, dysphagia, 'sticking sensation', belch, cough, regurgitation, nausea and vomiting.

After a 5 minute adaptation period, subjects were asked not to swallow for 30 seconds. This was required to measure resting (baseline) LOS pressure, the LOS margins, hiatus hernia as well as the upper oesophageal sphincter (UOS) relative to the nares.

5ml water swallows

Subjects were administered 5 ml water swallows (via a syringe) and were requested to swallow each bolus 'in one go' and to withhold further swallows briefly thereafter. The start and end of every swallow was 'framed' manually on the screen as the swallows progressed. If more than one swallow was noted and/or if other events that could interfere with analysis were identified (e.g. cough, vomit, sniff, laughter), the swallow frame was deleted. Each swallow used for analysis was separated by an interval of 20s. Where the study protocol required, 5-10 individual water swallows were collected and measurements were repeated in the supine left lateral position.

1 cc bread swallows

Bread was prepared in advance by applying low fat margarine on a slice of brown (untoasted) bread. Each slice was cut in half, apposed, the crusts were removed and the bread was cubed into equal 1 centimetre pieces. During the study subjects were instructed to chew one cube of bread very well. When ready, subjects were instructed to signal with a raised hand. When appropriate (i.e. no intervening swallows or no other oesophageal activity) the patient was asked to swallow the bolus 'in one go'. Up to 5 x 1 cc bread swallows were completed, and where the study protocol required, measurements were repeated in the supine left lateral position. The experience at St Thomas' Oesophageal Lab corroborated other studies in that more than one swallow was sometimes required to clear the pharynx when swallowing solids.[257] Therefore the number of pharyngeal deglutitions prior to effective distal oesophageal contraction was always recorded.

Free drinking (Multiple Water Swallows; MWS)

After water and bread swallows, where the study protocol required, subjects were requested to drink 200 ml of water freely through a straw without stopping. Drinking directly from the cup was discouraged as the larger volumes per swallow reduced the total number of swallows available for analysis. Furthermore, using a straw reduced movement of the head and neck during free drinking. If less than 200ml was drunk, the volume consumed was documented; although if they were able (and willing) the process was repeated. After completion of MWS, subjects were asked not to inhibit

their swallows as instructed during the 5 ml water or 1 cc bread protocol. Symptoms during or after completion were recorded deciduously.

Standardised Meal

Where the protocol required, and only if subjects consented, a standardised meal was provided which the patients were asked to consume at a comfortable pace. In view of the diversity in culture and religion of the patients referred from London area and beyond, meat-based products were excluded. Therefore the meal comprised of a standardised cheese and onion pasty (Ginsters, Cornwall, United Kingdom; 195 g, 500 Kcal, 34 g fat) and a 200 ml fruit-smoothie (ASDA Stores Limited, Leeds, United Kingdom; 100 Kcal, viscosity ~100 cPois.). (Figure 2.9) This was intended to be typical in volume, fat and calorie content of a standard western diet; a McDonald sausage McMuffin and milkshake. No patient in these studies was wheat or gluten intolerant. Participants were instructed before the study to report symptoms as soon as they occurred.

Figure 2.9 Standard meal (Ginster Cheese and Onion Pasty; 500 Kcal) and 200ml drink (ASDA lactose-free fruit smoothie; 100 Kcal)

Post meal observation

After the standardised meal, subjects were observed for a 10 minute period with the catheter in situ. Participants were instructed to behave (and swallow, belch etc.) normally. Again they were instructed to volunteer any symptoms if/when they occurred and close observation also permitted the investigator to mark any events that might not be volunteered by the patient (e.g. belch, rumination).

2.5 Analysis

The techniques described in this section are not clearly defined in the literature and vary from one published study and one lab to another; however these methods are employed by most expert users (Chicago, Nottingham, Royal London) and were employed for all studies in this thesis. Proprietary software (Manoview version 2.0, Sierra Scientific Instruments, Mountain View, CA) was used to analyse all HRM data. The investigator repeated the analysis of patients and healthy subjects one year after the index measurement while blind to demographics, presenting symptoms and history to confirm that measurements corroborated with initial findings.

2.5.1 Thermal compensation

After study completion, the catheter was removed and allowed to hang at room temperature/pressure for a few seconds. At this instant the catheter would still be at body temperature but all pressure sensors would be exposed to atmospheric pressure. The software automatically set this pressure as 'zero' and would apply sensor-specific thermal correction to the entire manometric data set. This *post-hoc* calibration would also compensate for measurement drift that may have appeared (Figure 2.10)

2.5.2 Swallow frame

Each 'swallow frame' was interrogated and extended or reduced in order to incorporate only one swallow (from just prior to pharyngeal relaxation to the LOS aftercontraction) per frame. For 5 ml water swallows, a frame that did not comprise only one, uninterrupted swallow was not included. (Figure 2.11a and b)

Solid swallows were not routinely framed during real time testing although they were marked manually for identification later. Therefore when being analysed, the original framed water swallows were deleted and new solid swallow frames were manually inserted. Unlike with water swallows, it was not uncommon if more than one pharyngeal swallow was required to propel a solid bolus. Only the contraction that followed the last pharyngeal swallow was framed and analysed. (Figure 2.12) The number of preceding pharyngeal swallows was counted and recorded. Pre-conditioning of repeated swallows was not assessed.

To facilitate comparison between water and solid swallows, a 30 mmHg isobaric contour was used to define peristaltic integrity for all swallows.[36,125] The isobaric contour is a line on the HRM plot which circumscribes all pressurised segments such that the pressure within is equal to or greater than a pre-specified pressure. (Figure 2.13) As alluded to in section 1.5.4 (HRM classification of oesophageal pathology), an isobaric contour of 30 mmHg is the most relevant for HRM classification schemes.[131] The qualitative and quantitative characteristics of every swallow were then described in turn after manual adjustment of oesophageal and LOS markers (Figures 2.11-15).

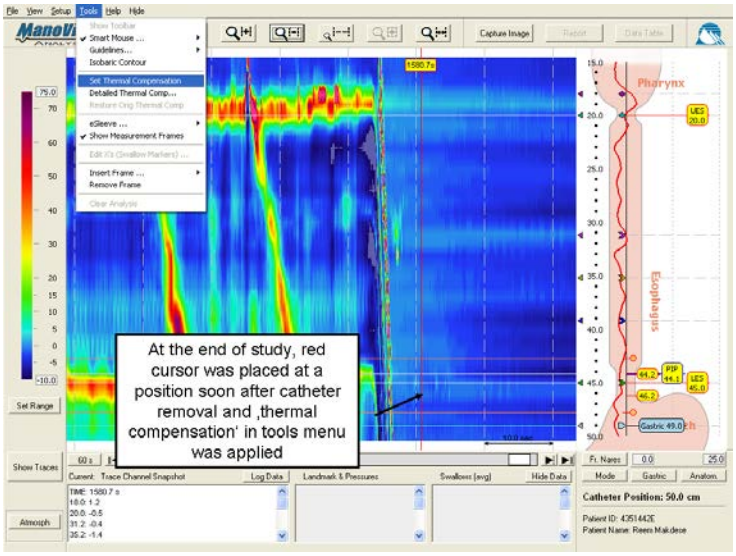


Figure 2.10 Thermal compensation process. The curser was placed at the end of the study and the thermal compensation function was applied.

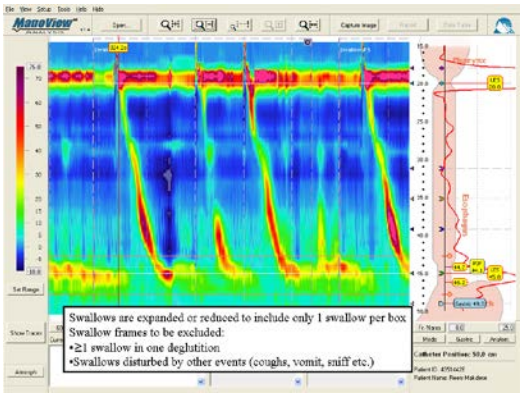


Figure 2.11a

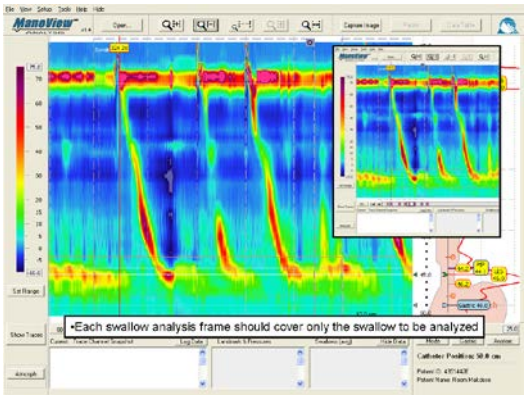


Figure 2.11b

Figure 2.11 Stepwise method of adjusting every HRM swallow frame to encompass only one, uninterrupted swallow.

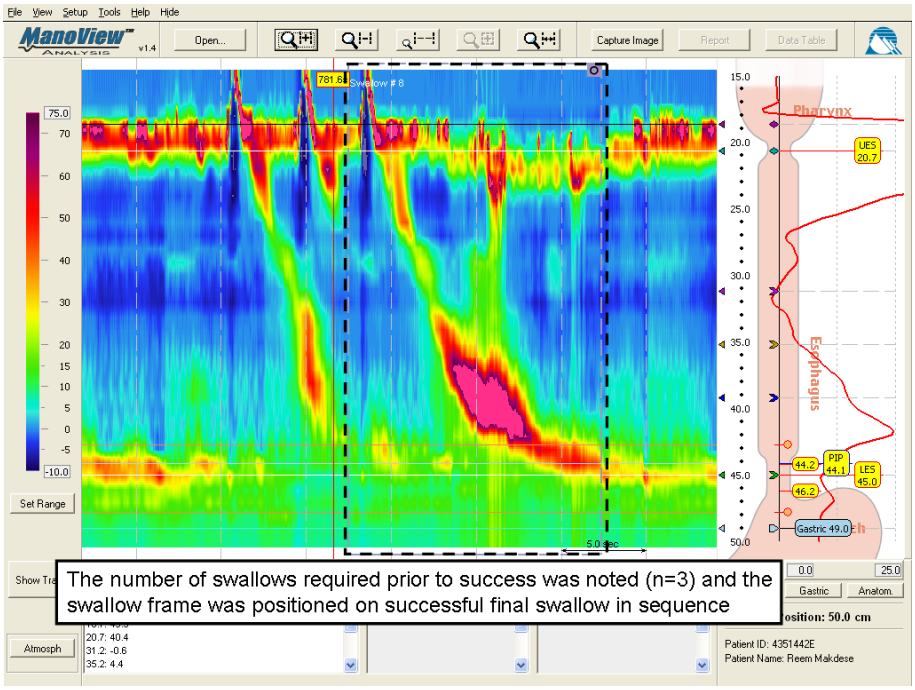


Figure 2.12. Solid swallow analysis. The swallow frame needed to be inserted manually. It encompassed only the final, (most) successful swallow.

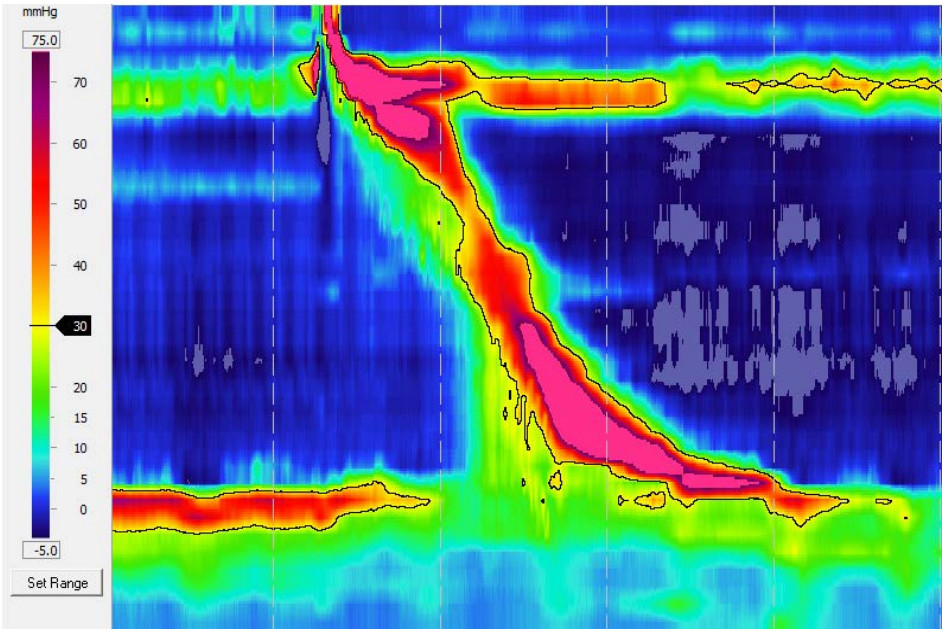


Figure 2.13 HRM with isobaric contour. A 30 mmHg isobaric contour (black line) circumscribes areas where pressure is equal to or exceeds 30 mmHg.

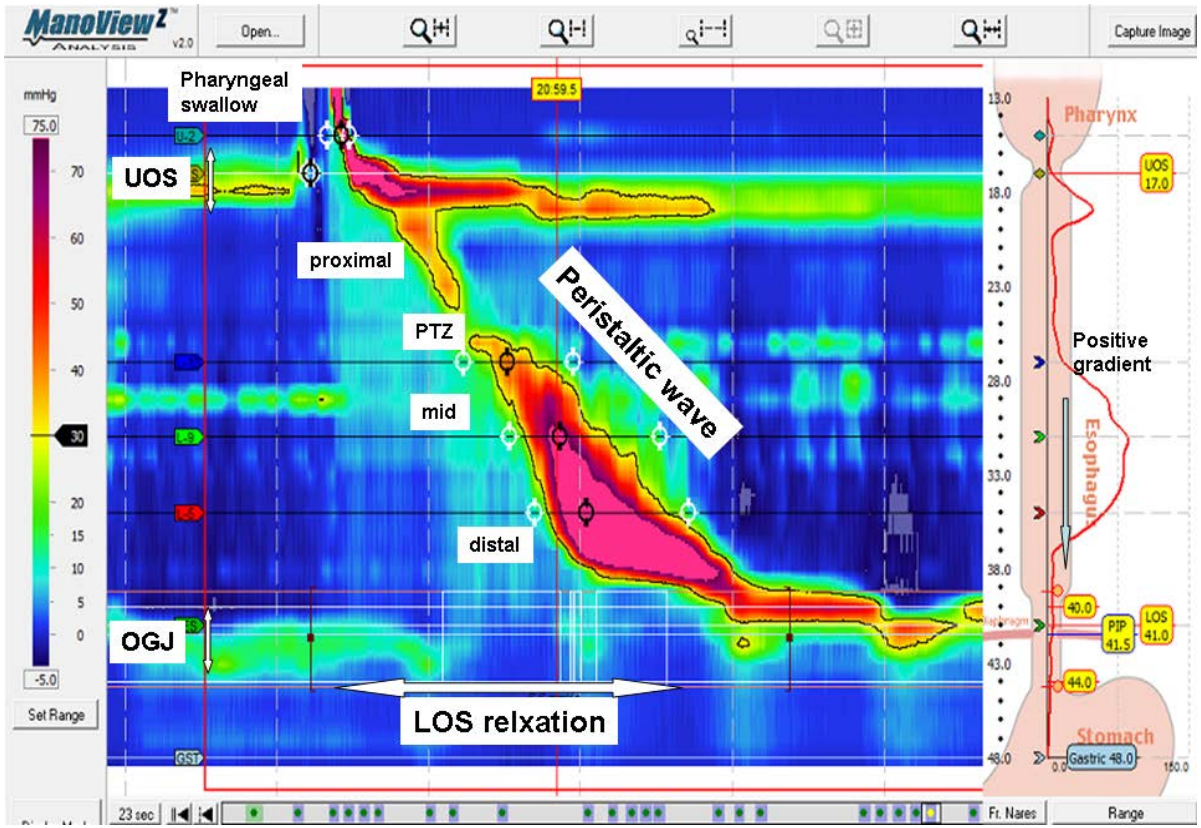


Figure 2.14 High resolution manometry swallow margins and landmarks. HRM of a normal swallow with pressure data presented as a spatiotemporal plot (STP). A 30 mmHg contour (black line) is superimposed on the image. Important landmarks are highlighted. The axial graph on the right shows the direction of flow relative to the pressure gradient at the site of the red curser (centre on the STP plot)

This trace is from a healthy volunteer presented in Chapter 4.

(UOS: Upper oesophageal sphincter; OGJ: Oesophago-gastric junction; PTZ: proximal transition zone).

2.5.3 Gastric reference

Distal sensors record the gastric pressure. This position can be manually defined. Variations in pressure with respiration increase if the sensor is too close to the diaphragm and during deep breathing. Therefore it is most reliable if the gastric reference is placed well within the gastric body. To standardise studies presented in this thesis, whenever possible the gastric reference was placed at a position at least 3 cm distal to the distal LOS margin. In the presence of a hiatus hernia, the gastric sensor was always placed out-with the distal hernia margin unless the hernia was exceedingly large (>5cm) in which case the gastric reference sensor was placed within the hernia.

2.5.4 Baseline LOS pressure and morphology

OGJ marker positions

Manoview automatically recognizes the upper and lower oesophageal sphincters by identifying the corresponding high pressure zones; however manual adjustment by the investigator was always required at baseline, especially if LOS sphincter pressure was reduced or hypertensive. Specifically, the principle LOS marker (yellow balloon in the axial trace of Figure 2.15) was placed at the maximum pressure point while the upper and lower LOS margins (proximal and distal yellow balloons above and below the principle LOS marker in Figure 2.15) were placed at the respective borders of the LOS. The principle, proximal and distal oesophageal LOS markers were also adjusted manually for every swallow to ensure accuracy.

By interpolating pressure data across the LOS, a 6cm ‘virtual sleeve’ (the e-sleeve) was derived from HRM data, thus providing a single measurement across the OGJ. This function is analogous to the ‘Dent sleeve’ used in water-perfused conventional manometry. It reduces the potential for inaccuracy that could arise from axial movement of the oesophagus by allowing for uninterrupted measurement of the maximum pressure along the length of the ‘virtual sleeve’. The e-sleeve makers (‘lollipops’ at the OGJ margin in the axial trace of Figure 2.15) were placed at either end of the LOS margins.

The transition point between the negative thoracic cavity and positive abdominal cavity (pressure inversion point; PIP) also required manual re-positioning at the start of analysis. This was considered to be the position of the diaphragm (cLOS).

LOS and PIP markers assisted in defining OGJ morphology (discussed in section 1.5.4). The presence of a HH was determined as a separation between the intrinsic LOS (iLOS) and crural diaphragm (cLOS/PIP). Although this separation was not fixed and sometimes appeared intermittently later in the study (e.g. during solid swallows or post-prandial period; Figure 2.16), by convention the presence/absence of a HH was classified only during baseline LOS measurement. In the presence of a HH, the e-sleeve markers were always placed at the upper border of the iLOS and below the PIP.

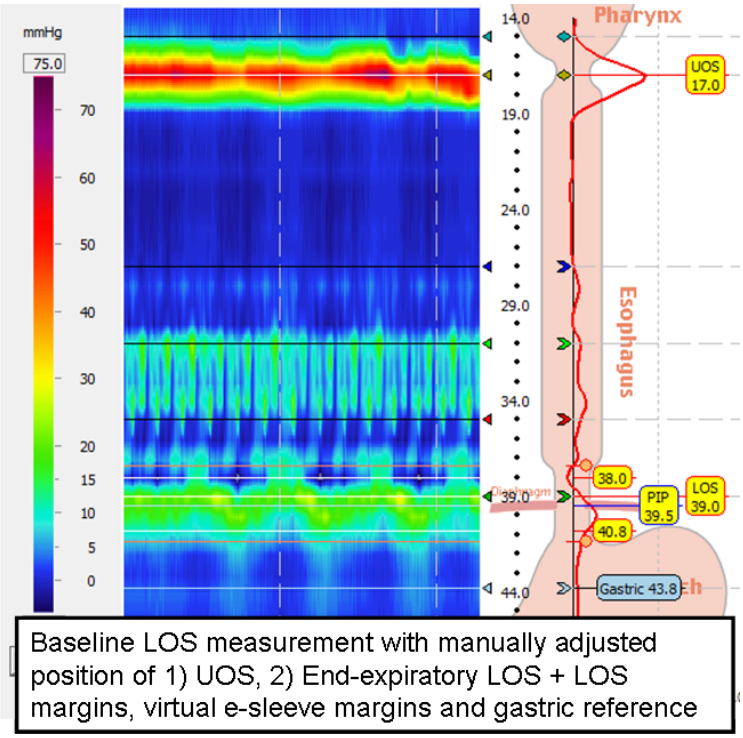


Figure 2.15 Upper oesophageal sphincter (UOS) and Lower oesophageal sphincter (LOS) margins using HRM. Note the principle (39 cm), proximal (38 cm) and distal (40.8 cm) LOS markers (yellow balloons) as well as the e-sleeve (orange lollipops) markers on the right of the axial trace. Also note the PIP and gastric reference makers.

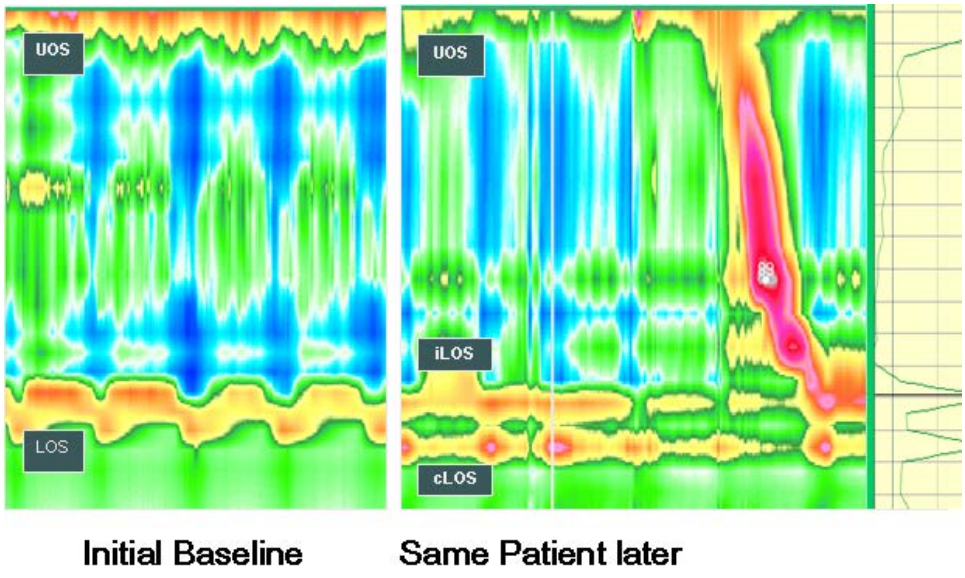


Figure 2.16 Transient hiatus hernia. Separation of the intrinsic and diaphragmatic lower oesophageal sphincter resulting in a transient hiatus hernia.

UOS: Upper oesophageal sphincter; LOS: Lower Oesophageal Sphincter,

iLOS: intrinsic LOS; cLOS: crural LOS.

(reproduced from M. Fox and A Bredenoord Gut March 2008[126])

2.5.5 Oesophageal peristalsis

HRM was analysed in terms of the proximal-, mid- and distal-oesophageal segmental contractions, as defined by Clouse and Staiano:[121,246]

(i) characteristic rise and fall of contractile pressure

(ii) peristalsis velocity,

(iii) duration of peristalsis

Once the investigator completed the manual adjustments, swallows required for analysis were framed. (Figure 2.11 and 2.12) Then every oesophageal swallow was scrutinised and markers were re-adjusted (e.g. upper and lower sphincters, contractility margins, etc.) as required. (Figure 2.17) The functional oesophageal length and the length of time required for a peristalsis event to pass were measured manually. (Figure 2.18) An automated analysis of basic parameters produced standard values for every individual which the investigator entered into a database. Then using the 30mmHg isobaric contour, the proximal (striated muscle) and mid/distal (smooth muscle) peristalsis segments were localised as was the pressure trough (PTZ).[246] The length, time interval, pressure and relation relative to the entire oesophagus (presented as a percentage) were manually calculated for every swallow. (see Chapter 5 for further detail).

A typical spatiotemporal plot with the axial graph of a healthy volunteer highlighting the isobaric contour at 30mmHg and showing the essential landmarks is presented in Figure 2.14.

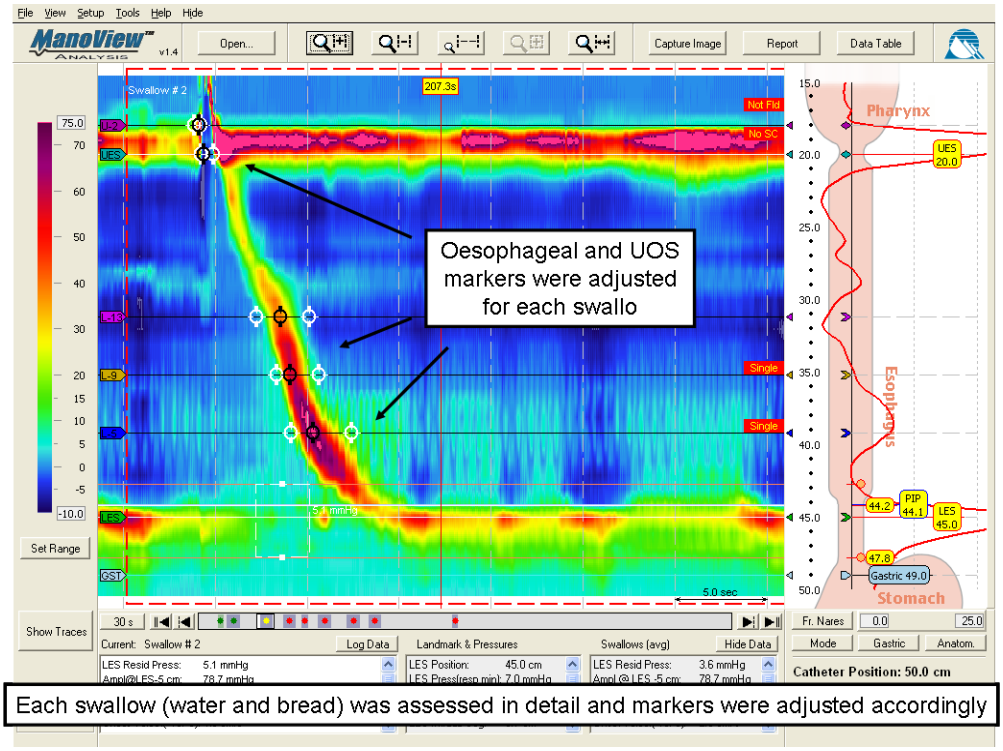


Figure 2.17 HRM manual adjustment. Automated markers were re-adjusted for every swallow

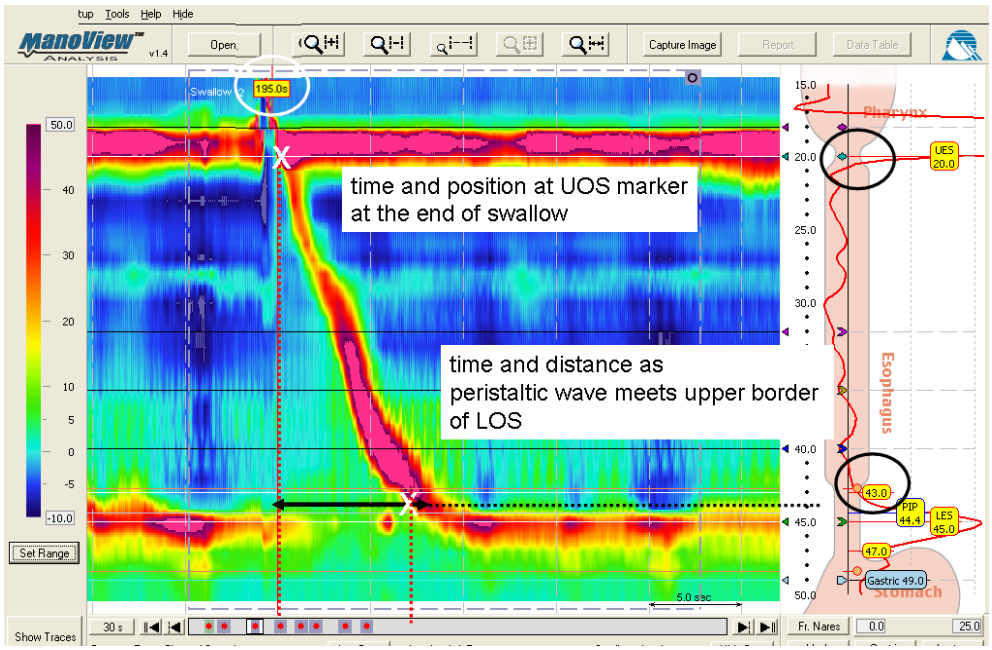


Figure 2.18 HRM manual measurement of oesophageal length and peristalsis time.

2.5.6 Standardised meal free drinking and post-meal observation analysis

A meal reproduces normal eating behaviour. It is more complex and laborious to analyse, there is no standardised technique and normative data is lacking. Therefore it is not routinely performed in Oesophageal centres. Novel analysis techniques for HRM while eating, drinking freely and for an observation period after are introduced in this thesis.

In regards to the standardised meal, in addition to individual metrics described above, the overall success or failure of oesophageal function following *every* pharyngeal swallow was assessed. Then each successful swallow was manually framed and adjusted in preparation for automated analysis. (Figure 2.19)

Three methods of analysis were undertaken during meal studies:

A) Quantitative analysis of successful 'framed' swallows. Analysis of these was analogous to single solid swallows (described in section 2.5.2)

B) Qualitative assessment of every pharyngeal and oesophageal activity
(*successful, ineffective, failed*)

C) Association of symptoms with dysmotility

The analysis technique for HRM while eating, drinking and during post-prandial observation will be described in detail in the methods sections of Chapters 5 and 6.

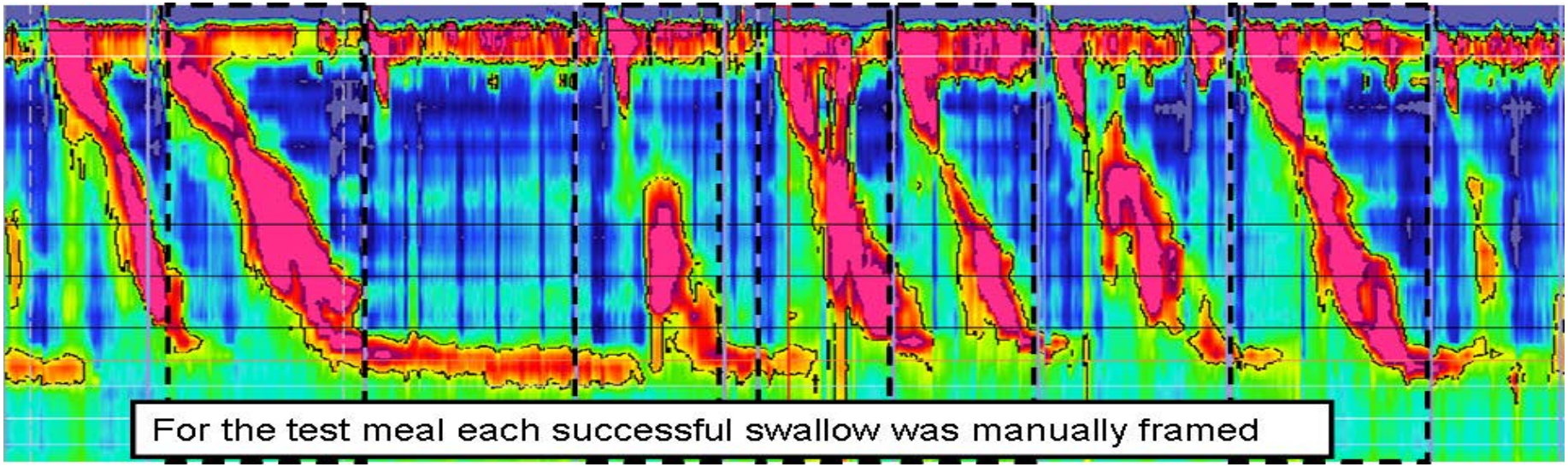


Figure 2.19 HRM during a meal. Spatiotemporal plot of swallows while eating. Successful swallows were framed in preparation for automated analysis.

2.5.7 Post-HRM pH monitoring

HRM studies were routinely followed by catheter-based pH monitoring. Studies were performed off acid reducing medication by the Digitrapper™ Slimline™ (Medtronic Inc., Shoreview, MN) system using the standard technique for preparation, investigation and analysis presented in section 2.1. Total reflux (percentage oesophageal acid exposure of less than 4) was the primary outcome measurement on which GORD diagnosis was based with a diagnostic cut-off of 4.2%. Symptoms were associated with reflux if they occurred within 2 minutes following a reflux event. Reflux Symptom Index (SI) was assessed with a diagnostic cut-off >50%.

2.6 Statistical analysis

Statistical analysis specific to each study will be discussed in detail in the corresponding chapters. Common statistical analysis techniques used for all studies are described here. All were performed using the SPSS 16.0 package for Windows, SPSS Inc., Chicago, Illinois, USA and Microsoft Office Excel 2003.

2.6.1 Ambulatory pH Monitoring

Student's t-test was used for quantitative variables and Fisher's exact test for qualitative variables. Mann-Whitney-U and Wilcoxon tests were used for nonparametric analysis of the TR, UR, SR SI and SAP between and within groups respectively. Results are reported as Median (Inter-quartile range). $P<0.05$ was considered statistically significant.

24 hour catheter-based study parameters were compared to 24 and 48 hour wireless pH monitoring measurements. Where required by the protocol the wireless study analysis was extended to 72 and 96 hours. For all prolonged studies (i.e. >24 hours), the single 'Worst day' and overall 'Average' measurements were used for the study duration. Furthermore for TR measurements, both cut-off values 4.2% and 5.3% were used for Bravo, and 4.2% was used for 24 hour catheter studies.

2.6.2 High Resolution Manometry

Student's t-test was used for quantitative variables. Mann-Whitney and Wilcoxon tests were used for nonparametric comparisons of quantitative swallow parameters between and within groups respectively. The Friedman test was used for analysis of

variance for multiple comparisons of nonparametric data within groups (i.e. comparing water, bread and test meal parameters within the same patient group). Pearson's coefficient (PC) assessed the strength of relationship between the frequency of effective swallows and the total time required to consume meals. $P<0.05$ was considered statistically significant. Results were reported as Median (Inter-quartile range) and Mean±Standard Error (Standard Deviation)

Normative values were presented as 5th and 95th percentiles. For water and bread swallows, coefficient of variation (CV) (standard deviation ÷ the mean for each subject x 100 expressed as a percent) was used to assess the intra-subject variability.

Chapter 3

Patient acceptance and clinical impact of Bravo monitoring in patients with previous failed catheter-based studies

3.0 Introduction

Standard ambulatory investigation for patients presenting with symptoms suggestive of reflux is routinely performed using the naso-oesophageal catheter (C-pH).[53,103] Limitations are intolerance to catheter insertion and inability to retain the catheter in-situ for 24 hours due to discomfort, gagging, nausea and vomiting. C-pH is also socially embarrassing and can have a negative impact on behaviour.[81,82,109] Bravo is an innovative, wireless pH monitoring system which is better tolerated and can measure for prolonged periods (48 hours).[103,85,104]

Patients who have Bravo performed are comprised of:

1) Those who are intolerant to C-pH
2) Those who have inconclusive results based on C-pH but have ongoing typical symptoms
3) Those with anatomical abnormalities (e.g. nasal septal defect) which preclude catheter-based testing.

The first two groups formulate the bulk of referrals to St Thomas's Hospital and indeed in the UK.[78,109] This chapter tries to answer two important questions:

I) Are patients that are intolerant to the nasal catheter able to tolerate the Bravo capsule insertion and the 48 hour study that follows?

II) Does the diagnostic yield in terms of pathological oesophageal acid exposure or reflux-symptom association justify investigation with Bravo?

3.1 Aims

It is assumed that as Bravo has a reduced impact on activities of daily living and that as studies are prolonged, Bravo collects more 'relevant' information for longer periods which will ultimately influence the diagnosis reached; however this theory has not yet been established. The aim of this study was to determine the tolerability of this group of patients to Bravo testing and to assess the diagnostic yield in terms of oesophageal acid exposure and reflux-symptom association over 48 hours in patients who have failed the nasal catheter.

3.2 Methods

(please refer to Methods Chapter 2; additional methodology specific for this study will be described here)

3.2.1 Study design

This was a prospective study which examined the technical success, patient satisfaction and results of 48 hour Bravo pH measurement in patients intolerant of the pH catheter, and compared them with a contemporaneous group of patients that tolerated 24 hour C-pH. All patients had C-pH and Bravo procedures performed at St Thomas' Hospital; however, prior to referral for Bravo the failed catheter-based studies had a widely variable referral base.

Hypothesis: 48 hour wireless pH monitoring is well tolerated and can identify GORD in patients who failed catheter-based pH monitoring.

3.2.2 Patients

Between March 2004 and January 2008, 2749 consecutive patients were referred to a tertiary centre (St Thomas' Hospital) for oesophageal manometry and pH studies. Results recorded in an electronic database and on paper records were collected. 2366 patients were referred for standard C-pH of which 615 cancelled or did not attend for their investigation. Of the 2134 patients remaining, 383 with known primary motility disorders on manometry or barium swallows (e.g. achalasia and nutcracker oesophagus) were excluded from the study. In the same period 185 patients were referred for Bravo of which 156 (84%) undertook the investigation. 154/156 (98.7%) of those investigated successfully completed a (standard) 48 hour Bravo study. The majority of these patients (134/156 (86%)) were offered Bravo after having failed 24 hour C-pH. (For inclusion/exclusion criteria please refer to Appendix 4)

110 consecutive patients from the same referral pool and with similar primary symptoms had C-pH performed and were provided with an un-validated tolerability questionnaire on their return to the oesophageal laboratory 24 hours later (Appendix 7). Those who failed manometry and C-pH and proceeded to Bravo also completed the same questionnaire on their return at 48 hours (Appendix 7). Endoscopic results, total percentage time pH drops below 4 in every 24 hours (Total reflux; TR) and Symptom Index (SI) were assessed in both groups.

3.2.3 Data analysis

Oesophageal acid exposure measurements

24 hour TR is the single most robust and reproducible diagnostic marker of GORD,[251] and is the most commonly used method for assessment in most laboratories and in the literature. Therefore identifying the 24 hour period with the highest acid exposure (TR) within the 48 hour catheter-free study was the primary outcome for this study. Average 48 hour results were also presented for comparison. Other parameters (e.g. number of reflux episodes) were not analysed separately to reduce the chance of type I errors related to multiple comparisons.

As described in Chapter 2, to improve diagnostic accuracy different cut-off values between C-pH and Bravo were employed for TR.[103,250,258] For categorical analysis, the effect of altering the cut-off value on diagnostic yield was assessed using:

(i) a standard cut-off value of 4.2% for both procedures, and

(ii) specific cut-off values of 4.2% for C-pH and 5.3% for Bravo in accordance with published values.[103,258]

Symptoms Index

The concept of measuring SI is discussed in detail in Chapter 2. Studies suggest that SI provides a clinically useful assessment of visceral sensitivity.[151] By convention a symptom event was considered to be associated with reflux if it occurred within a 2 minute time window after the reflux event.[253]

3.2.4 Statistical analysis

Student's *t*-test was used for quantitative variables (age) and the Fisher's exact test for qualitative variables (sex, endoscopy, categorical analysis of TR and SI). Mann-Whitney-U test was used for nonparametric analysis of TR and SI as well as to compare scores from the tolerability questionnaire between C-pH and Bravo. $P<0.05$ was considered statistically significant.

Assuming a 30% day to day variation in oesophageal acid exposure,[106] a sample size of 100 patients gives an 80% (beta 0.8) chance of detecting a 10% difference between C-pH and Bravo measurements.

3.3 Results

3.3.1 Patient demographics

Between March 2004 and January 2008, of the 1751 patients that had the catheter-based test with no known primary motility disorder, 883 (50%) had a diagnosis of gastro-oesophageal reflux disease based on a pathological TR (% time pH<4). In all 134/1751 (7.7%) could not tolerate the nasal catheter. This group of patients either did not tolerate the high resolution manometry (HRM) catheter (routinely performed prior to the pH study) or the pH nasal catheter itself. This is consistent with previously published data that 5-10% of patients are intolerant of catheter testing or fail to complete the 24 hour pH study.[51] Reasons for failure in this cohort were:

- intolerance of catheter insertion (HRM or C-pH) (84%)
- intolerance of the catheter after intubation (7%)
- vomiting of the catheter within the 24 hour monitoring period (9%)

A further 22 patients had Bravo performed during this time period but were *not* considered intolerant of the catheter and thus not included in the study. These patients had Bravo performed either because of ongoing symptoms despite a negative 24 hour test (11/22; the focus of Chapter 4), a contraindication to nasal catheterisation (e.g. recent rhinoplasty; 3/22) or an expressed desire against nasal intubation (8/22).

From the 134 patients who were catheter-intolerant and completed the Bravo procedure, the mean age was 46 (range 19-75; 58 males). These were compared to 110 consecutive C-pH controls with a mean age of 49 (range 16-85; 44 males). 94/134 (70%) Bravo patients and all C-pH patients completed the tolerability questionnaire. There was no difference in age (p=0.182) and sex (p=0.78) between these 2 groups.

Endoscopy results were recorded in 126/134 patients who underwent Bravo and 95/110 patients who underwent C-pH. (Table 3.1) There was no difference in endoscopic findings between the two groups (p=0.920). Almost all Bravo patients were on anti-secretory medication until one week prior to the procedure. Most of the C-pH group had their endoscopy performed at regional hospitals whereas the Bravo patients had their endoscopies performed at St Thomas' Hospital by an endoscopist who took particular note of mucosal disease prior to capsule deployment. For Bravo

insertion, the mean (range) doses for sedation in those who initially did not tolerate C-pH (midazolam 7mg (2-10mg) and fentanyl 67 mcg (50-150)) were higher than those for routine diagnostic endoscopy at St Thomas' (midazolam 4mg (0-5mg) and normally without fentanyl).

	Bravo		C-pH	
normal	81	64%	68	72%
Oesophagitis	37	29%	16	17%
LA classification A	23	18%	11	12%
LA classification B	14	11%	5	5%
Barrett's	5	4%	8	8%
Schatzki's ring	1	1%	1	1%
Stricture	2	2%	2	2%
n=	126		95	

Table 3.1 Endoscopy in Bravo and catheter study (C-pH) groups. Endoscopic findings showed no difference between Bravo and C-pH (p=0.922)

3.3.2 Oesophageal acid exposure

Data for TR was available for 129/134 consecutive Bravo patients and 102/110 consecutive C-pH patients. Continuous data analysis (Table 3.2a) showed a significantly higher median (IQR) TR between the average 48 hour Bravo (6.9) and 24 hour C-pH (4.1) groups (p=0.001). Categorical analysis (Table 3.2b) also showed a higher prevalence of pathological TR on at least one day during 48hr catheter-free pH monitoring using a standard cut-off value of 4.2% for both techniques (98/129 (76%) vs. 49/102 (48%) respectively; p<0.001). Using specific cut-off values of 5.3% for Bravo and 4.2% for C-pH, the prevalence of pathologic oesophageal acid exposure on at least one day remained higher in the Bravo group (92/129 (71%) vs. 49/102 (48%) respectively; p<0.001.) Average 48 hour results showed a similar finding with higher prevalence of oesophageal acid exposure in the Bravo group using 4.2% as a standard cut-off value (88/129 (68%); p=0.003) compared to C-pH; however this difference was not significant using a technique-specific cut-off of 5.3% for Bravo (74/128 (58%) vs. 49/102 (48%); p=0.179. (Table 3.3)

There was no systematic difference in the incidence of pathologic TR between the first and second day of Bravo measurements using 4.2% or 5.3% as cut-off values (Table 3.4a and b); 15/129 (11.6%) patients had a different outcome on day 1 and day 2 using 4.2% as a cut-off value and 16/129 (12.4%) using 5.3% as a cut-off value.

With Worst day analysis, there was a significant increase in the number of new patients diagnosed with GORD based on TR at 48 hours; 15 patients using 4.2% as a cut-off value (p=0.056) and up to 19 patients using 5.3% as a cut-off value (p≤0.05). Significance was lost with Average analysis; 5 additional patients had a positive TR using 4.2% as a cut-off value (p=0.600), 3 fewer patients compared to day 1 (p=0.900) and 3 additional patients compared to day 2 (p=0.800) using 5.3% as a cut-off value. (Table 3.4)

	Bravo %time pH<4 at 48hrs	C-pH %time pH<4
median	6.9	4.1
IQR	3-10.8	1.6-8.1
mw	0.001	

Table 3.2a

	Bravo %time pH<4 at 48hrs (cut-off 5.3%)		Bravo %time pH<4 at 48hrs (cut-off 4.2%)		C-pH %time pH<4 (cut-off 4.2%)	
pos	92	71%	98	76%	49	48%
neg	37	29%	31	24%	53	52%
n=	129				102	
X^2	0.0005		0.0001			

Table 3.2b

Table 3.2 Bravo vs. C-pH Total reflux (TR). (a) Continuous analysis of TR was higher for Bravo at 48 hours than 24 hour C-pH. (b) Categorical 'Worst Day' analysis of diagnostic yield applying different cut-off values for % time pH<4 to define GORD. Pathological TR was higher on at least one day in the 48 hour Bravo than the 24 hour C-pH group using either uniform (4.2%) or technique specific (5.3% and 4.2%) cut-off values for TR.

	Bravo %time pH<4 at 48hrs (cut-off 5.3%)		Bravo %time pH<4 at 48hrs (cut-off 4.2%)		C-pH %time pH<4 (cut-off 4.2%)	
pos	74	58%	88	68%	49	48%
neg	54	42%	41	32%	53	52%
n=	129		129		102	
X^2	0.179		0.003			

Table 3.3 Categorical analysis of 'Average' 48 hour Bravo analysis applying different cut-off values for TR to define gastro-oesophageal reflux disease. Pathologic oesophageal acid exposure was higher for 48 hour Bravo compared to 24 hour C-pH using a uniform TR cut-off value (4.2%) but not when using technique-specific TR cut-off values (5.3% and 4.2%).

TR 4.2% cut-off	Day 1			Day 2			48 hours Worst Day			48 hours Average	
pos	83	64.3%	pos	83	64.8%	pos	98	76.0%	pos	88	68.2%
neg	46	35.7%	neg	45	35.2%	neg	31	24.0%	neg	41	31.8%
total	129		total	128		total	129		total	129	
x^2	day 1 vs 2	1.000				x^2	vs day 1	0.056	x^2	vs day 1	0.060
							vs day 2	0.056		vs day 2	0.060

Table 3.4a

TR 5.3% cut-off	Day 1			Day 2			48 hours Worst Day			48 hours Average	
pos	76	58.9%	pos	71	55.5%	pos	92	71.3%	pos	74	57.4%
neg	53	41.1%	neg	57	44.5%	neg	37	28.7%	neg	54	41.9%
total	129		total	128		total	129		total	129	
x^2	day 1 vs 2	0.615				x^2	vs day 1	0.05	x^2	vs day 1	0.900
							vs day 2	0.01		vs day 2	0.800

Table 3.4b

Table 3.4 Categorical analysis for TR (total reflux) for Bravo on day 1 and day 2 as well at 48 hours using Worst day and Average analysis.
(a) TR cut-off value of 4.2% (b) TR cut-off value of 5.3%.

3.3.3 Symptom association

Not all patients experienced symptoms (e.g. heartburn, regurgitation, chest pain) during the study. Patients with no symptoms were not included in the symptom specific analysis; having no symptoms is not the same as having a negative symptom association

On continuous analysis (Table 3.5a) there was no significant difference in the median SI for heartburn (HB, the most common symptom) between the Bravo group at 48 hours (38.5%) and 24 hour C-pH (33.0%); p=0.80.

Categorical analysis (Table 3.5b) also showed no difference in SI for HB between Bravo (34/97) and C-pH (22/52) respectively; p=0.478. When SI for all potential reflux associated symptoms (HB, regurgitation, chest pain and cough) was pooled (Table 3.5c), there was also no significant difference between the Bravo (47/116) and C-pH ((32/65) groups; p=0.277; Table 3.5c).

	Bravo HB 48 hrs	C-pH HB 24 hrs
median	38.5	33.0
IQR	5.3-52.7	0-100
mw	0.800	

Table 3.5a

	Bravo HB 48 hrs		C-pH HB 24 hrs	
pos	34	35%	22	42%
neg	63	65%	30	58%
n=	97		52	
X^2	0.478			

Table 3.5b

	Bravo pooled SI 48 hrs		C-pH pooled SI 24 hrs	
pos	47	41%	32	49%
neg	69	59%	33	51%
n=	116		65	
X^2	0.277			

Table 3.5c

Table 3.5. Comparison between continuous and categorical analysis for symptom Symptom index (SI) between 48 hour Bravo and C-pH groups. a) Continuous analysis for heartburn (HB; there was no difference in median SI scores for HB with Bravo compared to C-pH. b) Categorical analysis for HB; there was no difference in diagnostic yield for GORD based on SI for HB with 48 Bravo compared to C-pH. c) Categorical analysis for pooled symptoms (HB, regurgitation, chest pain, cough); there was no difference in diagnostic yield for GORD based on SI between Bravo and C-pH when all symptoms were pooled.

3.3.4 Tolerance of Procedure

92 of the 134 consecutive Bravo patients and 102 of the 110 consecutive C-pH patients completed the tolerability questionnaire had TR data available for analysis. In those that answered the questionnaire, diagnostic yield in terms of continuous and categorical analysis of oesophageal acid exposure between Bravo and C-pH (Table 3.6) was similar to the overall results presented above. (Tables 3.2 and 3.3) The numbers of those who did not answer the questionnaire (Bravo n=36 and C-pH n=8) were too small for statistical comparison. Furthermore, there was no difference between those who answered the questionnaire and those who did not in terms of oesophageal acid exposure (Table 3.7a and b) or SI (Table 3.8a and b). For those who did answer the questionnaire, there was no difference in SI for heartburn, regurgitation or chest pain between day 1 and 2 (Table 3.9). Nor was there a difference between either day and 'Average' SI at 48 hours for HB (p=0.203 and p=0.692), regurgitation (p=0.637 and p=0.615) or chest pain (p=0.396 and p=0.764), nor when all symptoms were pooled. There was also no difference with SI for heartburn during Bravo at day 1 or 2 compared to 24 hour C-pH (p=1.000 and p=0.740).

	Bravo %time pH<4 at 48hrs	C-pH %time pH<4
median	6.1	4.1
IQR	2.2-10.7	1.6-8.1
mw	0.018	

Table 3.6a

	Bravo %time pH<4 at 48hrs (cut-off 5.3%)		Bravo %time pH<4 at 48hrs (cut-off 4.2%)		C-pH %time pH<4 (cut-off 4.2%)	
pos	63	69%	66	72%	49	48%
neg	29	32%	26	28%	53	52%
n=	92		92		102	
X^2	0.006		0.001			

Table 3.6b

	Bravo %time pH<4 at 48hrs (cut-off 5.3%)		Bravo %time pH<4 at 48hrs (cut-off 4.2%)		C-pH %time pH<4 at 48hrs (cut-off 4.2%)	
pos	49	53%	57	62%	49	48%
neg	43	47%	35	38%	53	52%
n=	92		92		102	
X^2	0.476		0.06			

Table 3.6c

Table 3.6. Total reflux (TR) for 48 hour Bravo and 24 hour C-pH for those who answered the questionnaire. a) Continuous analysis for TR between 48 hour Bravo and 24 hour C-pH. b) Categorical 'Worst day' analysis for TR between 48 hour Bravo and 24 hour C-pH. c) Categorical 'Average' analysis for TR between 48 hour Bravo and 24 hour C-pH.

	Questonniare Bravo TR at 48hrs (cut-off 5.3%)		No Questionnaire Bravo TR at 48hrs (cut-off 5.3%)	
pos	63	69%	29	81%
neg	29	32%	7	19%
	92		36	
X^2	0.196			

Table 3.7a

	Questonniare Bravo TR at 48hrs (cut-off 5.3%)		No Questionnaire Bravo TR at 48hrs (cut-off 5.3%)	
pos	49	53%	26	72%
neg	43	47%	10	28%
	92		36	
X^2	0.072			

Table 3.7b

Table 3.7 Questionnaire vs. No Questionnaire effect on TR. From the Bravo group, those who did and did not answer the questionnaires showed similar oesophageal acid exposure regardless of whether a) 'Worst day' or b) 'Average' analysis was used.
(TR: Total reflux; % time pH<4)

	Questionnaire HB at 48hrs		No Questionnaire HB at 48hrs	
pos	20	30%	12	46%
neg	47	70%	14	54%
	67		26	
X^2	0.152			

Table 3.8a.

	Questionnaire Pooled SI at 48hrs		No Questionnaire Pooled SI at 48hrs	
pos	30	38%	16	53%
neg	49	62%	14	47%
	79		30	
X^2	0.193			

Table 3.8b

Table 3.8. Questionnaire vs. No Questionnaire effect on Symptom Index (SI). 'Average' SI for a) heartburn (HB; the most common symptom) and (b) pooled symptoms (HB, regurgitation, chest pain) for 48 hour Bravo who answered and did not answer the questionnaire. Both showed no significant difference between the two groups.

	Heartburn Day 1		Heartburn Day 2		Heartburn 48hrs Worst day	
pos	25	41%	15	26%	31	46%
neg	36	59%	43	74%	36	54%
total	61		58		67	
X^2	0.120				v.s.Day 1 p=0.595 v.s.Day 2 p=0.025	

Table 3.9a

	Regurgitation Day 1		Regurgitation Day 2		Regurgitation 48hrs Worst day	
pos	13	34%	8	21%	20	43%
neg	25	66%	30	79%	27	57%
total	38		38		47	
X^2	0.305				v.s.Day 1 p=0.667 v.s.Day 2 p=0.367	

Table 3.9b

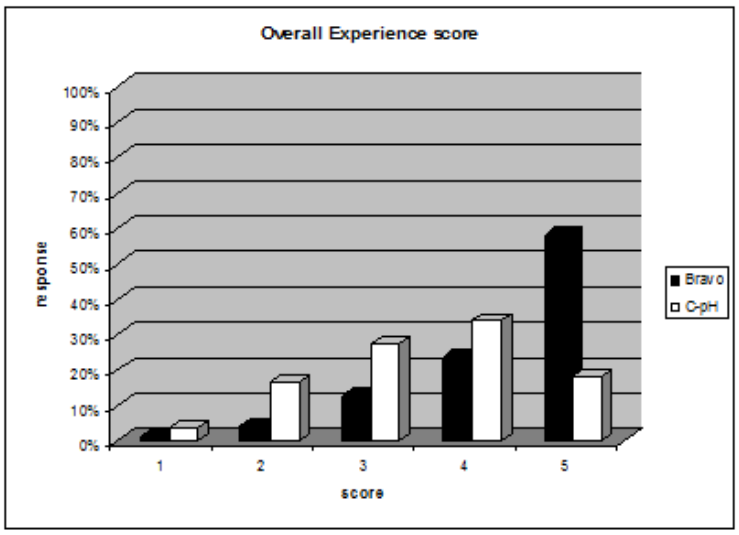
	Chest pain Day 1		Chest pain Day 2		Chest pain 48hrs Worst day	
pos	8	20%	6	15%	11	23%
neg	33	81%	34	85%	37	77%
total	41		40		48	
X^2	0.770				v.s.Day 1 p=0.798 v.s.Day 2 p=0.423	

Table 3.9c

Table 3.9 Bravo at day 1 with day 2 and 'Worst day' analysis at 48 hours for symptoms of a) heartburn, b) regurgitation and c) chest pain in those who answered the tolerability questionnaire.

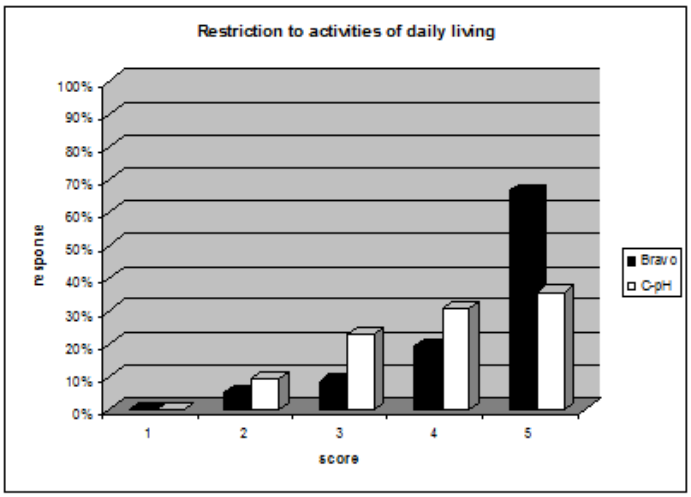
3.3.5 Tolerability questionnaire

The results of the tolerability questionnaire demonstrated a significant preference for the Bravo system compared to C-pH in almost all responses (Figures 3.1 to 3.4), with an overall satisfaction score of 4.4/5 vs. 3.5/5; $p<0.001$. All but one respondent that had undergone the Bravo study said they would recommend the procedure to another person compared to 73% that underwent C-pH ($p<0.001$). 96% patients that underwent both procedures preferred Bravo to C-pH despite the study being twice as long and requiring endoscopy. There was markedly less restriction of daily activities (Figure 3.2), throat discomfort (Figure 3.3), nasal discomfort and difficulty swallowing (Figure 3.4) during the Bravo study compared to C-pH ($p<0.001$ for all comparisons); however there was a similar amount of chest pain immediately following both procedures ($p=0.646$) (Figure 3.5). No complications occurred with the Bravo system (capsule retention, bleeding, perforation) and no capsule required endoscopic removal.



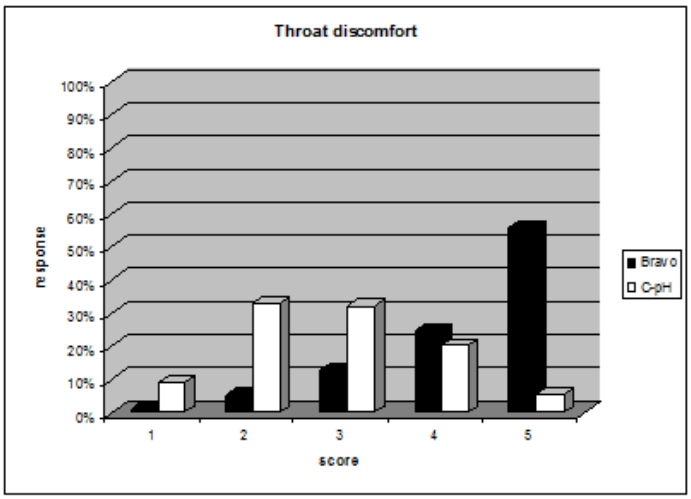
score	Bravo		C-pH	
1	1	1.1%	4	3.7%
2	4	4.3%	18	16.5%
3	12	12.9%	30	27.5%
4	22	23.7%	37	33.9%
5	54	58.1%	20	18.3%
	93		109	

Figure 3.1 Overall experience in Bravo and C-pH groups (1=very unhappy, 5=very satisfied). Patients favoured Bravo ($p<0.001$)



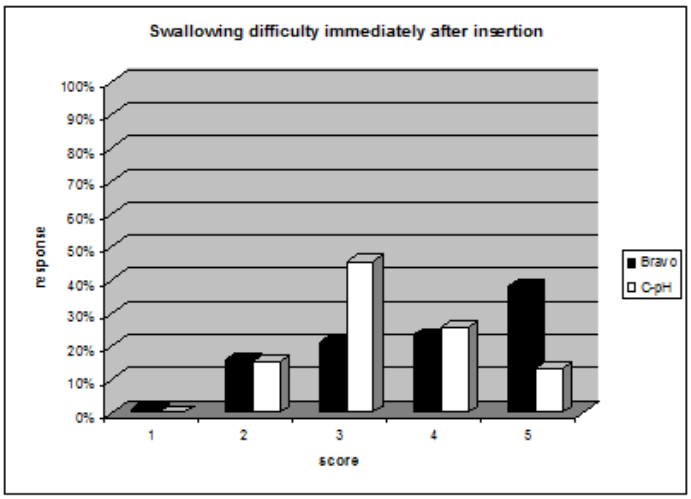
	Bravo		C-ph	
1	0	0.0%	0	0.0%
2	5	5.4%	10	9.7%
3	8	8.6%	24	23.3%
4	18	19.4%	32	31.1%
5	62	66.7%	37	35.9%
	93		103	

Figure 3.2 Restriction of everyday activities in Bravo and C-pH groups (1=very severe, 5=normal for patient). Patients favoured Bravo ($p<0.001$)



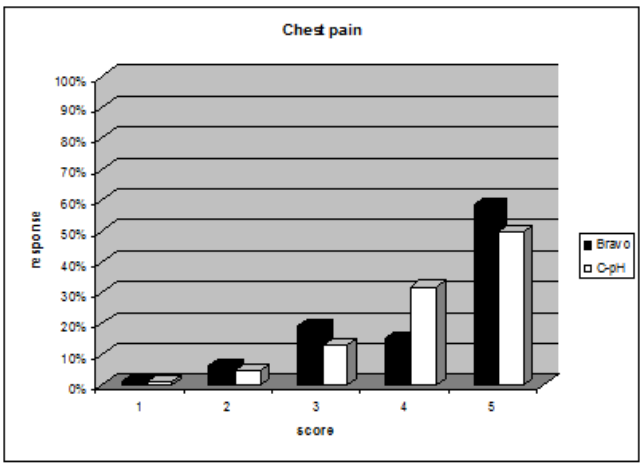
	Bravo		C-ph	
1	1	1.1%	10	9.2%
2	5	5.4%	36	33.0%
3	12	12.9%	35	32.1%
4	23	24.7%	22	20.2%
5	52	55.9%	6	5.5%
	93		109	

Figure 3.3 Throat discomfort in Bravo and C-pH groups. (1=very severe, 5=none). Patients favoured Bravo ($p<0.001$)



score	Bravo		C-ph	
1	1	1.1%	0	0.0%
2	15	16.0%	16	15.2%
3	20	21.3%	48	45.7%
4	22	23.4%	27	25.7%
5	36	38.3%	14	13.3%
	94		105	

Figure 3.4 Swallowing difficulty immediately after insertion of Bravo and C-pH (1=very severe/unable to swallow, 5=normal). Patients favoured Bravo (p=0.002).



score	Bravo		C-ph	
1	1	1.1%	1	0.9%
2	6	6.4%	5	4.7%
3	18	19.1%	14	13.1%
4	14	14.9%	34	31.8%
5	55	58.5%	53	49.5%
	94		107	

Figure 3.5. Chest pain immediately after insertion of Bravo and C-pH (1=very severe, 5=none). No difference between either system (p=0.646)

3.4 Summary of results

- Standard pH monitoring with a nasal catheter was not well tolerated by many patients and could lead to changes in diet and lifestyle that reduce reflux-provoking activities.
- Patient tolerance and satisfaction with the Bravo system was high with reduced restriction, discomfort and dysphagia, even in those who previously failed to tolerate catheter-based studies.
- The prevalence of pathological acid exposure was higher in the patients who underwent pH monitoring by the Bravo system (76% pathological TR on day 1 or 2) than an age and sex matched group that successfully completed the catheter-based study (48%; $p<0.01$).
- Patients that had failed to tolerate the nasal catheter study had no evidence of increased oesophageal sensitivity to reflux events as assessed by pooled symptom index ($p=0.28$).
- Had Bravo pH measurement not been available, many patients that had failed catheter-based testing would not have received a definitive diagnosis, and treatment choices (e.g. surgery) in this group may have been suboptimal.

3.5 Discussion

Studies suggest that between 5 and 10% of patients are intolerant of naso-gastric intubation or fail to complete 24 hour ambulatory catheter-based pH monitoring (C-pH).[51] In this cohort, wireless pH monitoring (Bravo) provides the means to obtain (or exclude) a definitive diagnosis of gastro-oesophageal reflux disease (GORD). The primary outcome of this study demonstrates that the Bravo technique is well tolerated and that pH measurement has a high diagnostic yield in these individuals.

There were no differences in baseline demographic, clinical characteristics or endoscopic findings between those that successfully completed 24 hour C-pH (n=110) and those that failed to tolerate the nasal catheter and underwent 48 hour Bravo (n=134). Patient tolerance was improved and activities of daily living were better preserved for Bravo compared to C-pH. (Figures 3.1-3.4) Although some studies have reported chest pain to be increased in patients undergoing the Bravo procedure,[82,103] pain was not described as being serious with very few requiring removal. The current study found little difference in chest pain between the two modalities immediately after the procedure; 6/94 (6.4%) and 5/107 (4.7%) patients complained of *severe* chest pain for Bravo and C-pH respectively (p=0.646). Thus far at St Thomas' Hospital, no patient has required the capsule to be removed for any reason over past 8 years of Bravo use. The relatively high doses of sedation required for Bravo capsule placement was likely due to intolerance of oro-pharyngeal manipulation in patients that failed to tolerate initial naso-pharyngeal intubation of the catheter-based studies..

On continuous analysis, as reported by previous comparative studies, the Total Reflux (Total % time pH <4; TR) was higher in the Bravo than the C-pH group (6.9% (3-10.8) vs. 4.1% (1.6-8.1); p=0.001). On categorical analysis, the prevalence of pathologic acid exposure on at least one 24 hour period (Worst day analysis) during the 48 hour Bravo study was higher than for the 24 hour C-pH measurement (Table 3.2) or for any individual 24 hour Bravo period (day 1 or 2) regardless of which diagnostic cut-off value was used (Table 3.4). Specifically, at 48 hours using a cut-off value for TR of 5.3% up to 19 new cases were found (p=0.01) and using a cut-ff value for TR of 4.2% 15 new cases were found (p=0.056). On other hand, if the diagnosis based on the 'Average' pH exposure over 48 hours was compared to 24 hour C-pH or

for any individual 24 hour Bravo period, then no significant increase in diagnostic yield was found (Tables 3.3 and 3.4). These findings were consistent with studies by Pandolfino et al and Scarpulla et al that showed analysis of the 'Worst day' increased diagnostic sensitivity in prolonged pH monitoring.[85,103] It is unclear if the diagnostic yield of 'Average' measurements with technique specific cut-off values would change if the Bravo study was prolonged further to 72 or 96 hours, a feature unique to Bravo. 96 hour studies would provide even more information (in terms of oesophageal acid exposure and symptoms) which should improve diagnostic confidence, especially in those with borderline results at 24 or 48 hours. This concept will be explored in Chapter 4 and a possible diagnostic algorithm will be re-visited in the Future directions Chapter 7.

16/129 (12.4%) and 15/129 (11.6%) patients had different outcomes on day 1 and day 2 using 5.3% and 4.2% cut-off values respectively. This is in keeping with a study by Gillies et al in which 10% of patients had their diagnosis changed when second day data was included.[83] Consistent with other studies,[103,250,259] the absolute number of positive tests between the first and second day did not change (Table 3.4). Rather the number of cases in which a positive reflux-symptom association can be established was increased with increased study duration.[260] Studies from St Thomas' Hospital and elsewhere have shown that prolonged study duration (up to 96 hours) reduced variation of oesophageal acid exposure measurements and improved test-retest reproducibility especially when using the more statistically robust Average analysis technique.[85,106,261,262] Although the majority of patients in this cohort only had 48 hour studies (as was the standard at that time) patients at St Thomas' Hospital are now routinely studied for up to 96 hours.

Despite the intolerance of Bravo patients to C-pH there was no significant difference in the SI for heartburn or for pooled reflux-related symptoms between 48 hour Bravo and 24 hour C-pH monitoring (Table 3.5). That is, despite discomfort from the catheter and intolerance, the association between perceived symptoms and reflux events did not change. Therefore, evidence from this study suggests that although the Bravo group had not tolerated the nasal catheter, in every other way they were representative of the same group (same amount of reflux symptom-association). These findings do not support the contention that patients that fail to tolerate C-pH

have ‘heightened sensitivity’ to distal oesophageal acid reflux. On the contrary, this group had *at least* as high a prevalence of pathological acid exposure as in C-pH (Table 3.2 and 3.3) and no evidence of visceral hypersensitivity as assessed by SI.[151] (Table 3.5) On the other hand, dual-sensor or Impedance-pH assessment to exclude proximal reflux sensitivity was not performed and is a weakness of this study.

Some Bravo patients did not complete the tolerability questionnaire; although not statistically significant, the minority of patients that did not complete the questionnaire had a numerically higher prevalence of pathological acid (Table 3.7).

3.6 Conclusion

In conclusion, this study compared a cohort of patients investigated by Bravo that had failed catheter pH monitoring to a contemporaneous, well-matched group of patients that successfully completed catheter studies. Patient satisfaction with Bravo pH monitoring was high and the technique was well tolerated, despite having previously failed to complete the catheter-based studies. There was no evidence to support that Bravo patients had higher oesophageal sensitivity to reflux events. Rather this group was unable to tolerate naso-pharyngeal intubation without sedation, and often required doses equivalent to those for interventional procedures.

This study has important clinical implications. Although no health economic data was provided, Bravo is known to entail a greater cost than C-pH. Furthermore, an additional visit to hospital is required for endoscopic placement. Nevertheless, had Bravo not been available, the many patients with pathological pH exposure would not have received a definitive diagnosis of GORD. This is likely to have impacted adversely on care and management decisions in many individuals, especially those under consideration for anti-reflux surgery. These findings support the recommendation that patients who fail to tolerate catheter-based testing should be offered catheter-free pH monitoring. In view of the improved tolerability and higher diagnostic yield for oesophageal acid exposure, 48 hour Bravo might be considered to be a better test than catheter-based studies. Furthermore, even more prolonged studies (72 or 96 hours) may have an impact on ‘Average analysis’ as more information becomes available. However such statements require evidence based on diagnostic outcome which was not achieved and was a major weakness of this study.

Chapter 4

Diagnostic yield of prolonged Bravo in patients with reflux symptoms and negative 24 hour catheter-based pH studies

4.0 Introduction

Chapter 1 and Chapter 3 described how the diagnostic yield of catheter-based 24 hour pH monitoring (C-pH) was diminished due to key limitations: tolerability, effect on daily activities and high day-to-day variability in acid exposure and symptoms.[81,83-86] Such shortcomings can lead to a false negative or false positive diagnosis of GORD. Prolonged measurement (up to 48 hours) increased diagnostic reproducibility and sensitivity, especially in patients with intermittent symptoms.[86] Furthermore, wireless monitoring was better tolerated and preferred by unselected patients.[84,103]

More than 90% of patients tolerate the nasal catheter. According to ROME III,[263] patients with negative results but ongoing typical symptoms are considered to have 'functional' oesophageal symptoms (i.e. functional heartburn); however given that one in three patients have a different diagnosis if the pH study is repeated on 2 separate days[51] and given its effect on patient behaviour, a negative, borderline or inconclusive result may be unreliable in the presence of ongoing typical symptoms. As a consequence patients with false-negative results may be denied appropriate therapy.

4.1 Aims

This study aimed to investigate whether prolonged (up to 96 hour) wireless pH monitoring improves the sensitivity of diagnosis and ability to identify reflux as a cause of symptoms in patients referred for a second opinion with ongoing symptoms suggestive of GORD but negative catheter-based pH results. Furthermore the clinical impact of prolonged Bravo was assessed at clinical follow-up 6–36 months after initiation of definitive therapy by the referrer based on the results of physiologic testing.

Hypothesis: 96 hour wireless pH monitoring can identify patients with pathological oesophageal acid exposure and in turn influence management decisions in those who previously had negative 24 hour catheter-based studies.

4.2 Methods

(please refer to Methods Chapter 2; additional methodology specific for this study will be described here)

4.2.1 Study design

This was a prospective study of patients who had successfully undergone 24 hour C-pH with negative results but continue to have ongoing typical symptoms suggestive of gastro-oesophageal reflux disease (GORD) with the purpose of assessing whether prolonged catheter-free pH monitoring (96 hour Bravo) changed the diagnosis and could aid in predicting outcome following therapy.

4.2.2 Patients

Between November 2006 and February 2010, 246 patients underwent wireless pH monitoring at St. Thomas' Hospital. Of those, 38 (15.4%) were referred following negative C-pH studies and ongoing 'typical' symptoms of reflux (heartburn, acid regurgitation). The majority of the catheter-based studies (35/38) had been performed at St Thomas' Hospital and had similar demographic and clinical characteristics as the patients in Chapter 3 and previously published studies from the same unit.[51,84] (Table 4.1) Acid-reducing medications were discontinued for at least 5-7 days prior to ambulatory studies as per the current British Society of Gastroenterology guidelines.[78] The decision to refer for Bravo was made by the referring clinician based on a negative oesophageal acid exposure on the C-pH study. (For inclusion/exclusion criteria please refer to Appendix 4)

Sedation

For the Bravo insertion, mean (range) doses for sedation in those who initially tolerated C-pH (midazolam 5mg (0-10mg) and fentanyl 63.5 mcg (0-100mcg)) was lower than for those who were intolerant to the nasal catheter presented in Chapter 3 (midazolam 7mg (2-10mg) and fentanyl 67 mcg (50-150)). Nevertheless, sedation remained higher than for diagnostic endoscopy at St Thomas' Hospital (midazolam 4mg (0-5mg) and normally without fentanyl). This is likely because the Bravo insertion technique required at least three consecutive endoscopy procedures to secure and confirm adherence (see Chapter 2).

Clinical follow-up

The clinical impact of pH measurement on management decisions and clinical outcome was assessed. Patient follow-up was performed a minimum of 6 months (median 24 (range 6-36) months) after initiation of definitive therapy. Medical or surgical therapy management decisions were made by the referring clinician after receiving results of prolonged Bravo. Patients rated their symptoms as 'good', 'moderate' or 'poor' during a telephone conversation.

4.2.3 Data analysis

Technical success and duration of prolonged Bravo was noted. Oesophageal acid exposure and reflux-symptom association were assessed as described previously. In both cases every 24 hour pH recording was analysed and categorized as being normal or pathological 'diagnostic of GORD' on the basis of the percentage time pH drops below 4 (Total reflux; TR)[251] and/or manually calculated reflux-symptom association (Symptom Index; SI or Symptom Association Probability; SAP). Details regarding TR, SI and SAP as well as the manual calculation of the latter metrics were described in Chapter 1, 2 and 3.

Furthermore, the effect of day-to-day variability of oesophageal acid exposure and (manual) symptom association on diagnostic yield based on 24, 48, 72 and 96 hour testing was calculated. If the Bravo capsule detached from the oesophagus before 96 hours, the 'final diagnosis' was based on the best available evidence from the complete pH and symptom data prior to detachment. To achieve this, the last result was carried forward in reporting thus providing a 'rolling cumulative' outcome. This is standard practice and ensured that the best available data was used in clinical decision making. Capsule drop off was assumed when there was a sudden fall to $pH < 2$ (suggestive of a drop into the stomach) followed by a rapid rise to $pH > 7$ as the capsule passed into the duodenum.

Oesophageal acid exposure

TR as well as acid reflux in the upright (UR) and supine (SR) positions were documented. 24 hour C-pH measurements were compared to Bravo at 24, 48, 72 and 96 hours. The 'Worst day' as well as the 'Average' 24, 48, 72 and 96 hour results

were presented. Because of the different TR normal values for C-pH and Bravo[103,258] for categorical analysis both: (i) a fixed diagnostic TR cut-off of 4.2% over the monitoring period for C-pH and Bravo studies (allows for direct comparisons) and (ii) a diagnostic cut-off of 4.2% (standard C-pH studies) and 5.3% (widely applied for Bravo studies) were applied to allow for technology-specific comparisons[103,258] (see Chapters 2 and 3)

Reflux-symptom association

Symptoms were associated with reflux if they occurred within a 2 minute time window of a reflux event. SI and SAP were calculated manually.[255] 'Worst day' as well as the 'Average' measurements were assessed as described in Chapter 3. For Bravo, analysis was performed by i) excluding those whose catheter dropped over time, and ii) including the last result prior to when the capsule dropped in which the last result was carried forward such that all patients were included in the final assessment ('Average cumulative' analysis). Analysis of individual typical symptoms (heartburn, regurgitation, chest pain) as well as the combination of all symptoms was recorded. The number of positive GORD diagnoses based on reflux-symptom association was compared for Bravo at 24, 48, 72 and 96 hours.

4.2.4 Statistical analysis

Student's *t*-test was used for quantitative variables, and Fisher's exact test for qualitative variables. Wilcoxon test was used for nonparametric analysis of TR, SI and SAP. Results were reported as median (inter-quartile range; IQR). $P<0.05$ was considered statistically significant.

4.3 Results

4.3.1 Patient demographics

38 consecutive patients with 'typical' symptoms of reflux and no diagnosis of GORD based on initial C-pH entered the study. Demographic, clinical and endoscopy data are detailed in Table 4.1. Typical symptoms of heartburn and acid regurgitation were reported by all patients. A proportion also reported less typical symptoms such as chest pain and cough (Table 4.1).

Bravo was performed successfully in all patients with the intention of acquiring a 96 hour pH recording. All patients completed at least 48 hours of Bravo. Capsule detachment occurred between 48 and 72 hours in 5 patients, and between 72 and 96 hours in 12 patients. Therefore complete 96 hour recordings were available in 21/38 (55%) patients. (Figure 4.1) No demographic or clinical factors (e.g. symptoms) were associated with early capsule detachment. Similar to patients in Chapter 3, no patient experienced more than mild swallowing difficulty or chest discomfort related to the procedure, and all patients described normal typical daily behaviour and diet during the Bravo study. No capsules needed to be removed prematurely. Reflux events were correlated with symptoms to achieve a reflux-symptom association assessment. (see Appendix 3 for diary log)

Total patients (n)		38	
Male:Female		13:25	
Median age (range)		42	17-75
		N	**%**
Presenting Symptoms	HB	32	84%
	Regurgitation	35	92%
	Chest Pain	27	71%
	Cough	5	13%
	Other (belch, dyspnoea)	7	18%
			Hiatus hernia
Endoscopic findings during Bravo study	Non erosive	27	8
	Grade A oesophagitis	10	2
	Barrett's oesophagus	1	1

Table 4.1 Characteristics and demographics of 38 patients who underwent wireless pH monitoring

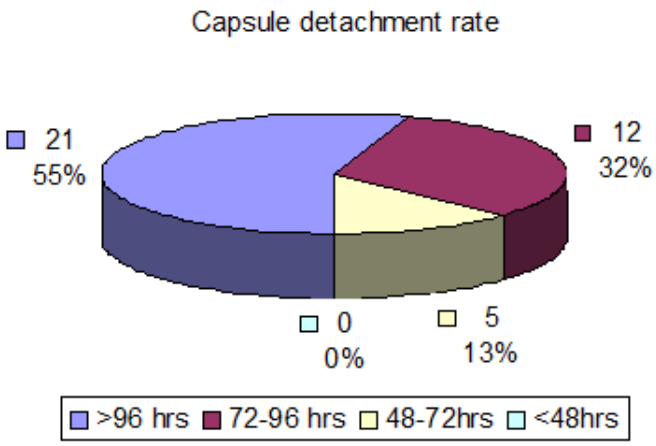


Figure 4.1 Detachment rate of capsules over 96 hours. No capsules detached <48 hours from insertion.

4.3.2 Oesophageal acid exposure

Similar to patients in Chapter 3, median oesophageal acid exposure was higher for Bravo at 24, 48, 72 and 96 hours than 24 hour catheter-based pH studies. ($p<0.05$) (Table 4.2)

Using the 'Average analysis' technique, prolonged wireless pH studies provided an objective GORD diagnosis based on pathological TR (using 5.3% cut-off) in 12/38, 12/38, 11/33 and 10/21 patients at 24, 48, 72 and 96 hours respectively; however this excluded patients who's capsule dropped pre-maturely in a sequential manner. Using a 'last result carried forward' approach such that results from all patients were considered, the 'Average cumulative' oesophageal acid exposure for Bravo was pathological at 96 hours in 14/38 (36.8%) using a diagnostic cut-off of 5.3% and 15/38 (39.5%) using a diagnostic cut-off of 4.2%. (Figure 4.2) If 'Worst day' analysis was applied, pathological TR was present on at least one day in 18/38 (47.4%) using a diagnostic cut-off of 5.3% and 22/38 (57.9%) using a diagnostic cut-off of 4.2%. (Figure 4.2)

Similar results were found if pathological acid exposure in the upright and supine positions were considered separately Table 4.3.

	C-pH 24hrs Median	(IQR)	Bravo 24hrs Median	(IQR)	Wilcoxon p values	Bravo 48hrs Median	(IQR)	Wilcoxon p values	Bravo 72hrs Median	(IQR)	Wilcoxon p values	Bravo 96hrs Median	(IQR)	Wilcoxon p values
TR	2.0	(1.2,3.0)	2.7	(0.9,6.6)	*	3.3	(1.4,6.7)	**	3.7	(1.4,6.7)	**	3.6	(1.5,6.8)	**
UR	3.1	(2.0,4.4)	3.3	(1.5,6.5)	†	3.6	(1.8,8.3)	*	3.9	(2.0,8.4)	**	3.9	(1.9,8.5.5)	**
SR	0.1	(0.0,0.4)	0.3	(0.0,2.9)	*	1.4	(0.0,6.6)	**	1.1	(0.2,4.6)	**	1.2	(0.2,5.8)	**

*† p<0.05, * p<0.01, **p<0.001 for comparison of Bravo (Wireless pH monitoring) against C-pH (Catheter-based pH monitoring)*

Table 4.2 Total reflux (TR) in Bravo vs. C-pH. C-pH recorded significantly less oesophageal acid exposure (TR) compared to Bravo at 24, 48, 72 and 96 hours. Similar findings were recorded in the upright (UR) and supine (SR) positions. There was no significant, systematic difference between 24, 48, 72 and 96 hour Bravo (all comparisons $p>0.1$).

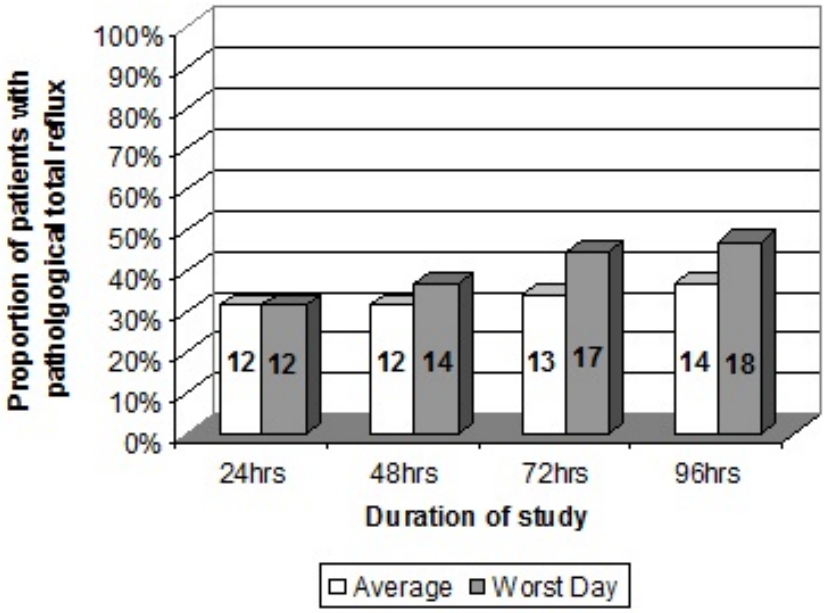


Figure 4.2a

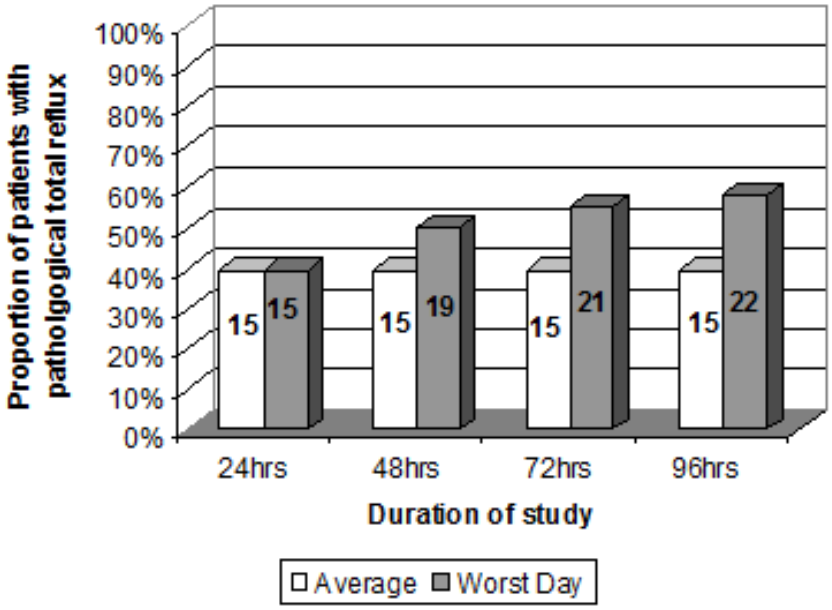


Figure 4.2b

Figure 4.2 TR using 'Average cumulative' and 'Worst day' analysis for Bravo. Results are presented as the proportion of patients with (a) pathological TR (cut-off of >5.3%) and (b) pathological TR (cut-off of >4.2%).

Oesophageal acid exposure in Upright position (Pathological acid exposure >8.15%)				
	24hrs	**48hrs**	**72hrs**	**96hrs**
Average				
Bravo pos	8 (21%)	10 (26%)	10 (26%)	11 (29%)
Worst Day				
Bravo pos	8 (21%)	12 (32%)	15 (39%)	16 (42%)
Oesophageal acid exposure in Supine position (Pathological acid exposure >3.45%)				
	24hrs	**48hrs**	**72hrs**	**96hrs**
Average				
Bravo pos	9 (24%)	12 (32%)	10 (30%)	12 (32%)
Worst Day				
Bravo pos	9 (24%)	17 (45%)	18 (47%)	19 (50%)

Table 4.3 Oesophageal acid exposure in the Upright and Supine positions. The 'Average cumulative' and 'Worst Day' analyses are presented for pathological ('Bravo pos') wireless oesophageal acid exposure at 24, 48, 72 and 96 hours.

4.3.3 Symptom-association

A median of 7 (IQR 4,15) symptom events were recorded by every patient on each day. All patients reported symptoms on at least one day during the study time period. The most common symptoms documented were heartburn (n=31), regurgitation (n=27) and chest pain (n=27). Atypical symptoms recorded included cough, sore throat, nausea and dyspnoea (n=7). Most patients recorded more than one type of symptom. (Table 4.4)

Symptom Index (SI)

When all reported symptoms were combined, 9/38 (24%) patients had a positive SI using 'Average cumulative' analysis at 96 hours (Figure 4.3 and Table 4.5). 'Worst day' analysis showed a positive SI in 23/38 (61%) patients (Figure 4.3 and Table 4.5). Similar results were observed also for individual symptoms (Table 4.6). Similar to the study presented in Chapter 3 (Table 3.9), no statistical difference was shown in SI for each individual day over time ($p>0.1$ for all).

Symptom Association Probability (SAP)

When combining all symptoms recorded during the Bravo study, 13/38 (34%) patients had a positive SAP using 'Average cumulative' analysis at 96 hours (Figure 4.3 and Table 4.5). 'Worst day' analysis showed a positive SAP in 24/38 (63%) patients (Figure 4.3 and Table 4.5). Similar results were observed also for individual symptoms (Table 4.7). Again, no statistical difference was shown in SAP for each individual day over time ($p>0.1$ for all) as was seen in Chapter 3 (Table 3.9).

Total # symptom events over 96hrs		1,806	
		Median	**IQR**
Daily median # of symptom events		7	(4,15)
Median number of symptoms (cumulative)	24hr	10	(4,15)
	48hr	20	(12,31)
	72hr	30	(14,43)
	96hr	30	(14,59)
			%
Proportion of patients reporting specific symptoms (n=38)	Heartburn	31	82%
	Acid regurgitation	27	71%
	Chest Pain	27	71%
	Combined Typical (HB+R+CP)	37	97%
	Atypical (belch, cough)	7	18%
Combination of symptoms reported during wireless pH-studies (initial 48hr)	0 Symptoms	1	
	1 Symptom	3	
	2 Symptoms	19	
	3 Symptoms	15	

Table 4.4 Symptoms reported during prolonged the prolonged Bravo study. Results are presented as median (inter-quartile range; IQR).

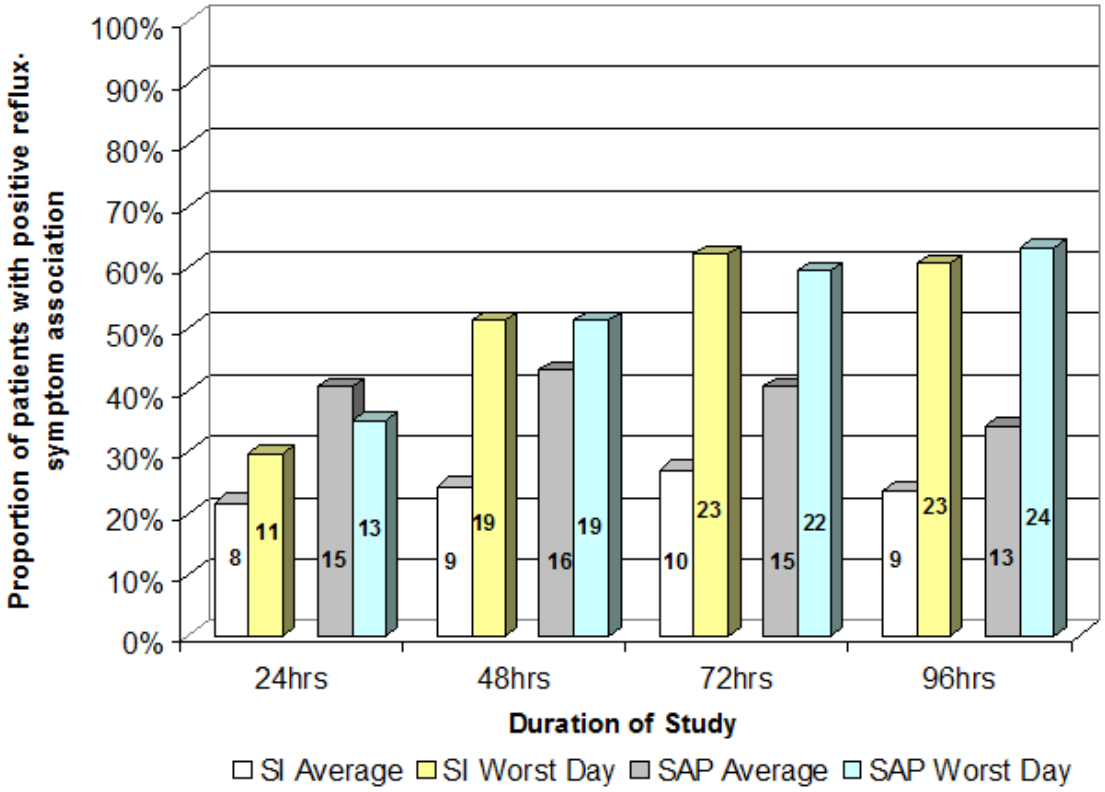


Figure 4.3 Proportion of patients with pathological Symptom Index (SI) and Symptom Association Probability (SAP) using 'Average' (rolling cumulative) and 'Worst day' analysis when all symptoms were combined during prolonged Bravo.

SI All Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	8	21.6%	9	24.3%	10	27.0%	9	23.7%
Bravo neg	29	78.4%	28	75.7%	27	73.0%	29	76.3%
No. pts reporting symptoms	37		37		37		38	
SI All Symptoms (Worst Day)								
Bravo pos	11	29.7%	19	51.4%	23	62.2%	23	60.5%
Bravo neg	26	70.3%	18	48.6%	14	37.8%	15	39.5%
No. pts reporting symptoms	37		37		37		38	
SAP All Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	15	40.5%	16	43.2%	15	40.5%	13	34.2%
Bravo neg	22	59.5%	21	56.8%	22	59.5%	25	65.8%
No. pts. Reporting symptoms	37		37		37		38	
SAP All Symptoms (Worst Day)								
Bravo pos	13	35.1%	19	51.4%	22	59.5%	24	63.2%
Bravo neg	24	64.9%	18	48.6%	15	40.5%	14	36.8%
No. pts. Reporting symptoms	37		37		37		38	

Table 4.5 Symptom Index (SI) and Symptom Association Probability (SAP) manually calculated with all symptoms combined. A pathological SI or SAP for any symptom was recorded as a positive result. The 'Average' and 'Worst Day' analyses are presented using the 'last result carried forward' method.

(Bravo = Wireless pH monitoring; HB = Heartburn; CP = Chest pain)

SI HB Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	8	28.6%	11	36.7%	11	35.5%	11	36.7%
Bravo neg	20	71.4%	19	63.3%	20	64.5%	19	63.3%
No. pts reporting symptoms	28		30		31		30	
SI HB Symptoms (Worst Day)								
Bravo pos	8	28.6%	13	43.3%	13	41.9%	14	45.2%
Bravo neg	20	71.4%	17	56.7%	18	58.1%	17	54.8%
No. pts reporting symptoms	28		30		31		31	

SI Regurgitation Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	7	31.8%	8	32.0%	8	30.8%	8	29.6%
Bravo neg	15	68.2%	17	68.0%	18	69.2%	19	70.4%
No. pts reporting symptoms	22		25		26		27	
SI Regurgitation Symptoms (Worst Day)								
Bravo pos	7	31.8%	11	44.0%	14	53.8%	14	51.9%
Bravo neg	15	68.2%	14	56.0%	12	46.2%	13	48.1%
No. pts reporting symptoms	22		25		26		27	

SI CP Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	1	5.3%	4	16.7%	5	20.0%	5	18.5%
Bravo neg	18	94.7%	20	83.3%	20	80.0%	22	81.5%
No. pts reporting symptoms	19		24		25		27	
SI CP Symptoms (Worst Day)								
Bravo pos	1	5.3%	5	20.8%	9	36.0%	9	33.3%
Bravo neg	18	94.7%	19	79.2%	16	64.0%	18	66.7%
No. pts reporting symptoms	19		24		25		27	

Table 4.6 Symptom Index (SI) calculated for individual symptoms. The 'Average' and 'Worst Day' (pathologic SI for any symptom rated as a positive result) analyses are presented using the 'last result carried forward' method.

(Bravo = Wireless pH monitoring; HB = Heartburn; CP = Chest pain)

SAP HB Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	6	21.4%	9	30.0%	9	29.0%	6	19.4%
Bravo neg	22	78.6%	21	70.0%	22	71.0%	25	80.6%
No. pts. Reporting symptoms	28		30		31		31	
SAP HB Symptoms (Worst Day)								
Bravo pos	6	21%	10	33.3%	11	35.5%	12	38.7%
Bravo neg	22	79%	20	66.7%	20	64.5%	19	61.3%
No. pts. Reporting symptoms	28		30		31		31	

SAP Regurgitation Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	8	36.4%	9	37.5%	7	26.9%	6	22.2%
Bravo neg	14	63.6%	15	62.5%	19	73.1%	21	77.8%
No. pts. Reporting symptoms	22		24		26		27	
SAP Regurgitation Symptoms (Worst Day)								
Bravo pos	8	36.4%	10	41.7%	11	42.3%	12	44.4%
Bravo neg	14	63.6%	14	58.3%	15	57.7%	15	55.6%
No. pts. Reporting symptoms	22		24		26		27	

SAP CP Symptoms (Cumulative)								
	24hrs		48hrs		72hrs		96hrs	
Bravo pos	2	11.1%	5	20.8%	5	20.0%	6	22.2%
Bravo neg	16	88.9%	19	79.2%	20	80.0%	21	77.8%
No. pts. Reporting symptoms	18		24		25		27	
SAP CP Symptoms (Worst Day)								
Bravo pos	2	11.1%	6	25.0%	10	40.0%	10	37.0%
Bravo neg	16	88.9%	18	75.0%	15	60.0%	17	63.0%
No. pts. Reporting symptoms	18		24		25		27	

Table 4.7 Symptom Association Probability (SAP) calculated for individual symptoms. The 'Average' and 'Worst Day' (pathologic SAP for any symptom rated as a positive result) analyses are presented using the 'last result carried forward' method.

(Bravo = Wireless pH monitoring; HB = Heartburn; CP = Chest pain)

4.3.4 Agreement of reflux-symptom association assessments

Diagnostic agreement between a positive SI *and* SAP on rolling (Average cumulative) analysis incorporated fewer patients than that based on the 'any single day' (Worst day) analysis. At the end of the prolonged Bravo study 5 patients had a positive SI *and* SAP using 'Average cumulative' analysis and 19 patients had a positive SI *and* SAP using 'Worst day' analysis. (Figure 4.4)

GORD diagnosis based on acid exposure *and* reflux-symptom association

Agreement between positive oesophageal acid exposure (TR) *and* reflux-symptom association (SI *or* SAP) increased the overall number of patients diagnosed with GORD. Applying 'Average cumulative' analysis, 8/38 (21%) patients had a GORD diagnosis based on a positive TR *as well as* a positive SI *or* SAP. However, 23/38 (61%) patients had a GORD diagnosis based on *either* 'Average' positive TR *or* positive reflux-symptom association. (Figure 4.5a)

Applying 'Worst day' analysis, 17/38 (45%) patients had a GORD diagnosis based on a pathological TR *as well as* a positive SI *or* SAP on any day. On the other hand, 29/38 (76%) patients had a GORD diagnosis based on *either* a positive TR *or* a positive SI *or* SAP on any day. (Figure 4.5b) It was on this basis that most referrers formulated their management decisions.

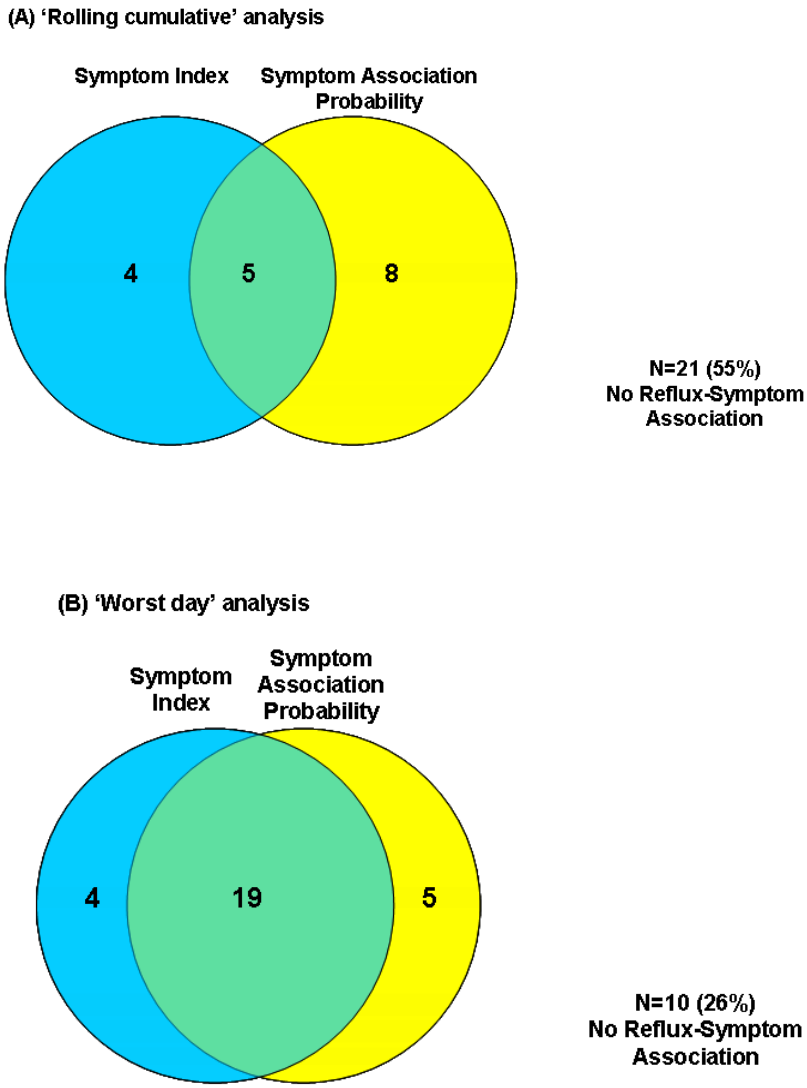


Figure 4.4 Agreement of positive Symptom Index *and* Symptom Association Probability using (A) 'Average cumulative' analysis and (B) 'Worst day' analysis.

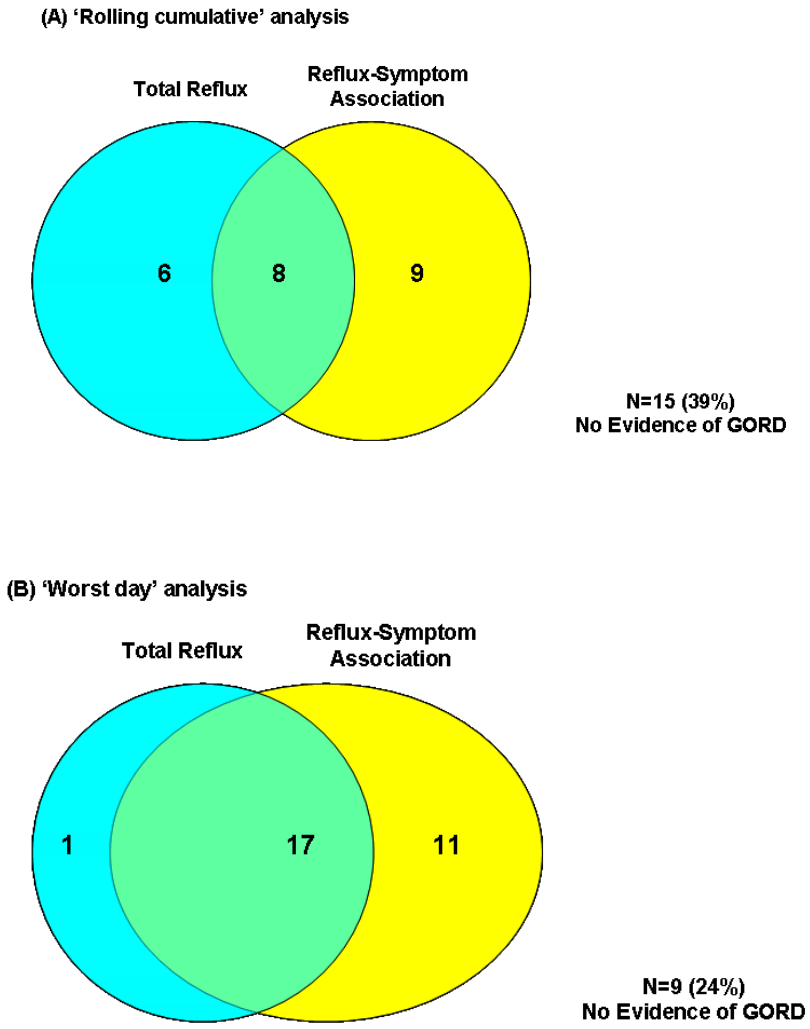


Figure 4.5 Diagnostic yield for GORD based on positive Total Reflux *and* any symptom association (SI *or* SAP) using (a) 'Average cumulative' analysis and (b) 'Worst day' analysis.

4.3.5 Outcomes

Treatment decisions were made by the referrer and were based on 'Worst day' analysis for acid exposure *or* reflux-symptom association following prolonged Bravo monitoring. Outcome at least 6 months after initiation of definitive therapy was available for 33/38 (87%) patients.

Medical therapy

26/38 (68%) patients had conservative therapy provided by the referring physician. This comprised of optimising either:

i) acid-reducing medication (e.g. esomeprazole BD) (n=19; 5 lost to follow-up), or

ii) dietary/lifestyle modification with or without alternative antacid therapy (n=2).

The outcome for 21/26 patients was assessed at a median 24 months (range 12–36 months). 9 patients had an improvement in symptoms and 12 described a poor outcome. Overall 9/9 (100%) and 9/12 (75%) had a GORD diagnosis based on pathological oesophageal acid exposure or positive reflux-symptom association respectively (p=0.361).

Surgical therapy

12/38 (32%) patients had anti-reflux surgery performed and outcome was assessed at a median 24 months (range 6 months (2 patients) – 36 months). Of these patients, 9/12 had a positive diagnosis based on pathological oesophageal acid exposure (positive TR) and all also had a positive reflux-symptom association (positive SI or SAP). 1 other patient had pathological supine reflux only on day two and the SI for regurgitation was positive only on day three. Two patients had surgery despite negative 'formal' pH studies studies. Out of the latter two, one had pathological supine reflux only and a large hiatus hernia on endoscopy. The other had ongoing symptoms suggestive of non-acid food and fluid regurgitation with normal endoscopy and manometry with a recording of 119 symptoms over 96 hours most directly after meals. This was almost certainly suggestive of rumination, a voluntary yet subconscious repetitive learned habit resulting in a sudden increase in intra-abdominal pressure which overcomes the lower oesophageal sphincter basal tone and forces gastric contents into the oesophagus, and often, into the mouth.[128,141] (Figure 1.8)

At follow-up, 10 patients had a good outcome and 2 patients had persistent reflux symptoms and were awaiting repeat pH studies. Of these 8 of the 10 with good outcome and 2 of the 2 with poor outcome had a clear positive diagnosis of GORD (p=1.0). Similarly, 7 of the 10 patients with good outcome and both patients with poor outcome had had at least a partial (50%) response to PPI therapy prior to anti-reflux surgery. A further patient with a good initial result had new-onset dysphagia after 6 months that was shown to be due to a trans-diaphragmatic herniation of the wrap

4.4 Summary of results

- Catheter-based pH studies may be confounded by modified patient behaviour and day-to-day variation in reflux events and symptoms.
- Wireless pH studies were better tolerated than catheter studies with reduced impact on patient activity and oral intake
- Prolonged wireless pH monitoring had a high diagnostic yield of picking up pathological oesophageal acid exposure in patients with negative catheter-based pH studies as it reduced false-negative diagnoses; 47.4% and 36.8% using 'Worst Day' and 'Average' analysis respectively.
- Prolonged wireless pH monitoring increased diagnostic sensitivity for significant reflux-symptom association; 73.7% and 44.7% had a positive SI or SAP using 'Worst Day' and 'Average' analysis respectively.
- Using 'Worst-day' and 'Average' analysis, 76% and 61% patients were diagnosed with reflux disease based on either pathological acid exposure *or* reflux-symptom association.
- 10/12 Patients diagnosed with GORD based on prolonged wireless pH studies following a negative catheter-based study had good outcomes following anti-reflux surgery.

4.5 Discussion

4.5.1 Oesophageal acid exposure and symptom association

This prospective study reports a high diagnostic yield of prolonged (up to 96 hour) wireless pH monitoring (Bravo) in patients with typical reflux symptoms in whom the initial 24 hour catheter-based pH studies (C-pH) were negative. Patients diagnosed on the basis of this investigation and referred for definitive, surgical management had good outcomes.

The demographic and clinical profile of the 38 patients recruited for this study (Table 4.1) was typical of the larger group referred for pH studies at St Thomas' Hospital.[51,84] Similar to previous reports from the same unit,[84] capsule deployment was successful in all patients and no adverse events were reported. Furthermore all patients reported normal food and fluid intake and all were able to undergo their routine daily activities. At least 48 hours of continuous pH recording were obtained in all subjects and 21/38 (55%) completed 96 hours, with a median capsule adherence of 72 hours (3 days) (Figure 4.1) Although this was higher than that reported in other studies presented in the literature (e.g. Scarpulla et al reported a 41% completion rate to 96 hours)[85] it was lower than the most recent internal audit at St Thomas' Oesophageal lab in which 70% capsules were retained by day 4 with a 10% drop off from day 2.[261] (Figure 2.3) This was likely multi-factorial:

i) improved experience with the device deployment over the years, and

ii) manufacturers that supply Bravo changed ownership and upgraded the delivery device on at least 2 occasions over the previous 6 years; however it is important to note that there have been *no* changes to the capsule mechanics, signalling and receiver pick up, nor with the proprietary software (Polygram net) used for this study during the same time period.

Examination of the data provided insight into how prolonged Bravo studies might have increased diagnostic yield compared to 24 hour C-pH. 12/38 patients had pathological acid exposure (TR) in the first 24 and 48 hours (using 'Average' analysis), and 12/48 and 14/38 patients had pathological TR in the first 24 and 48 hours using 'Worst day' analysis. From 48 to 96 hours there was a further increase in diagnostic yield based on pH measurement with 2 additional cases using 'Average'

and 6 additional cases using 'Worst day' analysis (Figure 4.2a). This was most pronounced with supine reflux (SR) in which pathological SR from day to day changed with the greatest frequency: 9/38 (day 1), 12/38 (day 2), 6/33 (day 3) and 4/21 (day 4), and when using 'Worst day' analysis up to 50% patients became positive by 96 hours. (Table 4.3) 8 patients had pathological acid reflux on at least 3 of the 4 days. Increasing the study from one to two days increased the median number of combined symptoms reported from 10 to 20 episodes/day (Table 4.4) and approximately doubled the number of reflux episodes and symptom episodes available for association. Prolonging the study further to 3 and 4 days increased the number of symptoms by a median of 10 episodes. Therefore although prolonging the study produced a modest increase in positive Total reflux from day 1 to day 4 using 'Average' analysis, the increase was pronounced with 'Worst day' analysis and, consistent with previous studies, this increase was greatest for reflux-symptom association.[86] (Figure 4.3 and Table 4.3-4.7) These findings imply that reflux events and symptom events have a wide day-to-day variability and by increasing the duration of study more reflux events and symptom events are available for analysis and this in turn increases the diagnostic yield compared to standard 24 hour C-pH studies.

Interestingly 'Average cumulative' analysis results occasionally showed a drop in the numbers of those diagnosed with GORD. This was most notably seen for supine reflux (Table 4.3) where SR dropped from 12 patients with pathological findings at 48 hours to 10 patients at 72 hours. This phenomenon was also recognised during reflux-symptom association assessment (Figure 4.3 and Table 4.5) where SI dropped from 10 patients with pathology at 72 hours to 9 at 96 hours and SAP dropped from 16 patients with abnormal results at 48 hours to 13 at 96 hours. Again, the wide variability in reflux and symptom events from day to day would account for this discrepancy. As this calculation is cumulative, a pathological SR on one night in a borderline case may 'dilute' the averaged measurement over time. Therefore, 'Average analysis' may be considered a more conservative assessment of pathology which increases the *specificity* for identifying true GORD; a positive result is more likely to be true whilst borderline results are normalised over time. On the other hand, 'Worst day' analysis is more likely to identify those with intermittent symptoms therefore increasing the *sensitivity* for identifying GORD, although this also increases the likelihood of false positive results. This is in keeping with Scarpulla et al[85] who

showed that whilst 'Worst day' analysis maximised diagnostic yield at 48 hours, 'Average' measurement was more likely to improve diagnostic accuracy. A consensus on which technique is most appropriate has not yet been reached in the literature, nor was the focus of this study to answer this question; therefore both results were presented in this thesis to inform the reader.

4.5.2 Diagnostic agreement

The causes of symptoms are non-specific and patients commonly reported various symptoms in response to reflux events. Heartburn was the most common symptom recorded; however the majority of patients complained of at least 2 different symptoms per day with a median number of *any* symptoms reported of 7 (4,15) per day and 30 (14,59) over the entire study (Table 4.4). No patient remained symptom free during the 96 hour monitoring period. Using 'Average cumulative' analysis for *all* symptoms, 9/38 (24%) and 13/38 (34%) patients had a positive SI and SAP at the end of the study respectively (Figure 4.3 and Table 4.5). The effect of individual symptoms was also presented for SI and SAP and these too showed a similar trend. (Tables 4.6 & 4.7) As expected, pathological findings were more common using 'Worst day' analysis as 23/38 (61%) and 24/38 (63%) patients had a positive SI and SAP at 96 hours respectively.

A diagnosis of GORD based on positive SI *or* SAP was present in 17/38 (45%) patients using the 'Average' analysis and in 28/38 (74%) patients using 'Worst day' analysis (Figure 4.4). Again, the increase in diagnostic yield over time was greater with 'Worst day' than 'Average' analysis. When measurements of oesophageal acid exposure (TR) *and* reflux-symptom association (SI *or* SAP) were combined, the diagnostic yield was high with 61% receiving a diagnosis of GORD based on well-validated criteria (described in Chapter 1 and Chapter 2) and a conservative analysis method using the 'Average cumulative' technique. This yield increased further to 76% if the diagnosis was based on 'Worst day' analysis. It is important to re-iterate that 'Worst day' analysis is the most often quoted in the literature [103] and is used in clinical practice at St Thomas' Hospital as well as other major oesophageal centres (personal communication with the Chicago group at Northwestern University Hospital and Digestive Diseases Centre, Nottingham). Furthermore, clinicians

commonly formulate their therapeutic decisions based on 'Worst day' results of either TR (even isolated pathological SR) and/or reflux-symptom association.

4.5.3 Outcome

The clinical utility of any investigation and diagnosis is based on its ability to guide effective management. Studies have shown that pathologic oesophageal acid exposure or reflux-symptom association on pH testing predicts a positive outcome after definitive anti-reflux surgery.[77,175,264] Furthermore, guidelines recommend against surgical management in the absence of a definitive GORD diagnosis.[78,265] Thus a false negative result on pH testing can have important consequences for the management of this patient group and it may be more prudent to 'rule out' than 'rule in' a diagnosis of GORD in this patient group.[266]

This study reported excellent control of reflux symptoms following anti-reflux surgery in 10/12 patients with a negative C-pH study that then received a definitive, positive GORD diagnosis on Bravo. The two patients that did not have good symptom control had persistent acid reflux-like symptoms. In contrast, only 34% reported a good response to optimal conservative therapy (all had GORD); whereas 66% had a poor response or were lost to follow-up (9 had GORD). Three of these patients with objective evidence of GORD were awaiting surgery and one with evidence also of delayed gastric emptying was being treated with prokinetic drugs. The remaining 5 patients with poor response to PPI had a diagnosis of GORD based on positive reflux-symptom association to only a few reflux events. Studies have shown that the outcome of surgery is similar in patients with GORD diagnosis based on pathological acid exposure or positive reflux-symptom association.[77,264] However, whilst such individuals may profit from surgery, the primary problem in such cases is likely to be visceral hypersensitivity rather than reflux *per se* [151] and, similar to the patients without GORD, it is likely that in these cases treatment with low-dose tricyclic antidepressants or directed at reducing chronic visceral pain was preferred by the referring clinician. Preliminary reports suggest that a high symptom index on prolonged pH-symptom monitoring predicts a *poor* outcome to Omeprazole treatment,[151] but numbers in this study were too small to test this hypothesis.

This study included 10 patients with mild (Grade A) erosive disease. However, studies have shown that oesophagitis LA grade A is not uncommon in asymptomatic individuals and that grade A oesophagitis and endoscopy negative reflux disease (ENRD) have similar clinical characteristics and physiology (manometry and pH studies).[267] Moreover, longitudinal studies have shown an important cross-over between LA grade A oesophagitis and ENRD groups on repeated endoscopic studies.[267] Therefore, the presence of grade A oesophagitis does not preclude the need for investigation and should not be considered diagnostic for GORD. In line with published guidelines, it is the policy at St Thomas' Hospital to proceed with anti-reflux surgery only in the presence of pathological results on physiologic testing,[78,268] even in the presence of pathologic endoscopic findings. Although all patients who proceeded to anti-reflux surgery had an initial trial of acid-reducing medication, to the best of the investigator's knowledge the decision for escalation to surgery by the majority of referring clinicians/surgeons out with St Thomas' Hospital also adhered to the same published national guidelines.

4.6 Conclusion

In conclusion, prolonged wireless pH monitoring had an important clinical impact in patients presenting with typical reflux symptoms but negative catheter-based studies. Additionally, without a definitive diagnosis, many in this patient group would not have received effective therapy based on C-pH results. In most centres at least one in three patients that undergo C-pH studies have a negative test result.[51] This study suggested that if a false-negative diagnosis was suspected, and especially if there was a possibility that behaviour may have been modified (catheter discomfort or social embarrassment), then prolonged wireless pH studies should be considered. Moreover, in patients with intermittent reflux and symptom events on C-pH studies, prolonged wireless pH monitoring is likely to be the optimal investigation for GORD diagnosis.

Chapter 5

Normative values and inter-observer agreement for liquid and solid bolus swallows in upright and supine positions and normative values for free drinking, standardised meal and post meal observation in the upright seated position as assessed by oesophageal high resolution manometry

5.0 Introduction

Conventional manometry (with 5-8 pressure sensors) uses point pressure measurements to define peristaltic activity and oesophago-gastric junction (OGJ) relaxation. Abnormal function is characterised by a few basic patterns: hypertensive, hypotensive ('ineffective') or absent contractility, oesophageal spasm and incomplete OGJ relaxation.[78,113] Studies have shown that if normal oesophageal function is preserved, bolus transport is almost always successful; however in the presence of dysmotility, apart from spasm and hypotensive contractility, the association between bolus transport and symptoms is weak with conventional manometry alone.[46] Moreover reproducibility and inter-observer agreement for classification of pathology using conventional manometry is only fair.[116,269] Many diagnoses based on conventional manometry are subjective, sometimes based as much on patient presentation as objective measurements of contractility[126] making the clinical significance of oesophageal dysmotility uncertain.

High Resolution Manometry (HRM), with spatiotemporal presentation of pressure data using 21-36 sensors (Figure 5.1), increases the accuracy with which oesophageal bolus transport can be predicted and is more sensitive to clinically relevant dysfunction that induce symptoms.[111,126] HRM-based oesophageal and OGJ normative values have been established for 75 asymptomatic controls using a 36 sensor, solid-state Manoview catheter.[125,131,247] Swallows were performed in the supine position using 10 x 5 ml water swallows therefore allowing for direct comparison with conventional manometry. However swallowing in the supine position does not reflect normal behaviour and may be poorly tolerated by patients with 'true pathology' and impaired bolus transport. Furthermore, symptoms are rarely reproduced after swallowing small volumes of water.[126] The inclusion of upright solid bolus swallows increases the sensitivity for identifying clinically relevant dysmotility;[126,270-274] although this has not yet entered routine clinical practice because standardised methodology and normative values are lacking. Although reproducing normal swallow behaviour is more likely to induce typical symptoms and provide information that is more relevant to the patient, so far no studies have routinely used normal eating and drinking to recognise oesophageal pathology. An assessment of oesophageal and lower oesophageal behaviour after a meal may also be of value as it may provide insight into the mechanisms of reflux in health and disease.

Normal values for single liquid and solid swallows in the upright position have been reported using a 21 sensor water-perfused HRM catheter, a system which is no longer widely used in clinical practice.[36] Moreover, only basic parameters were reported (contractile length, pressure and velocity in the proximal, mid and distal oesophagus) and data was not analysed with HRM metrics and methodology currently in use.[36] An assessment of normal swallow behaviour (free drinking, eating a standardised meal and post-meal observation) have never been formally assessed with 36 sensor HRM.

Solid swallows differ from standard water as they are not always transported through the oesophagus with a single peristaltic contraction. Pouderoux et al showed that even in healthy subjects up to 4 swallows may be required to achieve clearance of a single solid bolus.[257] Solid swallows produce complex pressure activity and, as the analysis methodology has not yet been standardised, inter-investigator agreement is impaired.[126,272-274]

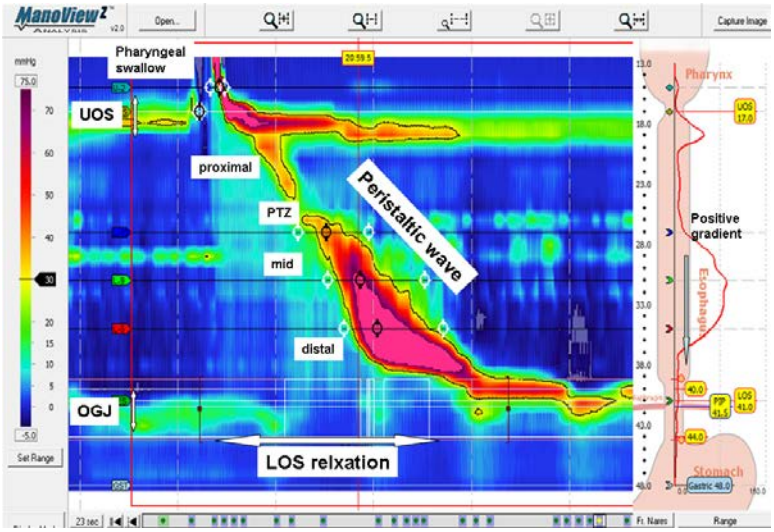


Figure 5.1 High resolution manometry of a normal swallow. Important oesophageal landmarks are highlighted. A 30 mmHg isobaric contour was applied. The axial graph on the right shows the direction of flow relative to the pressure gradient at the site of the red curser (centre). Lower oesophageal sphincter margins are demarcated in the axial graph on the right.
(UOS: Upper oesophageal sphincter, OGJ: Oesophago-gastric junction, PTZ: proximal transition zone).

5.1 Aims

This chapter aims to provide a stepwise analysis of oesophageal function utilising current and novel metrics customised for the analysis of 36 sensor solid state HRM.[131] A standardised methodology was proposed and normative values were presented for single liquid and solid bolus swallows in the upright and supine positions. An assessment of inter-observer agreement then provided confidence that these techniques are reproducible. Peristalsis and OGJ function of HRM pressure data in both positions and bolus consistencies were compared. In some, swallow assessment during a standardised meal followed single bolus testing. Normative values were presented and results were compared to upright single bolus water and bread swallows. Finally a standardised methodology and reference values were presented for free drinking as well as a ten minute post-prandial observation period. A close record of symptoms reproduced during and after the meal was made.

Hypothesis: The challenge of increasing bolus volume and consistency while swallowing will influence oesophageal function in a predictable and reproducible manner in healthy individuals.

5.2 Methods

(please refer to Methods Chapter 2; additional methodology specific for this study will be described here)

5.2.1 Study design

This was a single centre prospective study of normal subjects performed at the St Thomas' Hospital Oesophageal Laboratory. Each subject underwent High Resolution Manometry (HRM) in the upright seated and supine (left lateral) position. This provided reference values and compared oesophageal peristalsis and OGJ function in both positions for liquid and solid swallows. Additionally, inter-observer agreement of measurements derived from HRM pressure data was reported. A subset of the same patients proceeded to assessment during free-drinking and eating (standardised test meal) followed by a 10 minute post-meal observation period. All studies were performed in the upright position from which further normative values were derived. Oesophageal peristalsis and OGJ function of swallows during water, bread and test meal swallows were compared. A stepwise analysis of oesophageal function utilizing metrics customized for the analysis of HRM data was applied.[131]

Ethics was approved by the St Thomas' Hospital Research Ethics Committee in February 2008 (REC reference 07/Q0702/3) – see Appendix 9

5.2.2 Subjects

23 healthy volunteers were recruited (11 Male: 12 Female; age range 20-56 years, BMI range 18-33). None had symptoms suggestive of reflux disease or oesophageal dysfunction, nor were any taking medication known to affect oesophageal function or gastric acid secretion. (For inclusion/exclusion criteria please refer to Appendix 8)

Swallows

After a 5 minute adaptation period, subjects were provided with 5 swallows of 5 ml water administered with a syringe (liquid swallows) followed by 5 swallows of 1 cm cube (1 cc) of bread (solid swallows). Measurements were repeated in the upright

(seated) and supine (left lateral) positions. Further details of methods were described in section 2.4 of Chapter 2.

10 of the 23 asymptomatic healthy volunteers (6 Male: 4 Female, age range 20-45) provided consent also to drink 200 ml of water freely (Multiple Water Swallows; MWS) followed by a standardised test meal. These subjects were then observed for a 10 minute post-prandial period. All were instructed to inform the examiner of symptoms as soon as they occurred. Further details of methods were described in section 2.4 of Chapter 2.

5.2.3 Data analysis

Swallow effectiveness for single swallows and the test meal

Following pharyngeal deglutination, a swallow was classified as peristaltic or non-peristaltic. Non-peristaltic swallows were divided into

i) Ineffective peristalsis - defined as either ≥3 cm spasm (>5.3 cm/s; simultaneous contraction) or ≥3 cm break in the 30 mmHg contraction front of the distal oesophageal segment (Figure 5.2)

or

ii) Failed peristalsis - defined as either absent peristalsis or if contractility was <3 cm in length in the distal oesophageal segment within the 30 mmHg isobaric contour.

In regards to failed peristalsis, as in previous publications,[36,125,247,275] distal oesophageal parameters could not be calculated and the swallow was not included in summary calculations of normative values; however for the test meal, the number of ineffective and failed swallows was included in the overall assessment of 'swallow effectiveness' and was defined as the frequency of:

i) Successful swallows
ii) Ineffective swallows
iii) Failed swallows

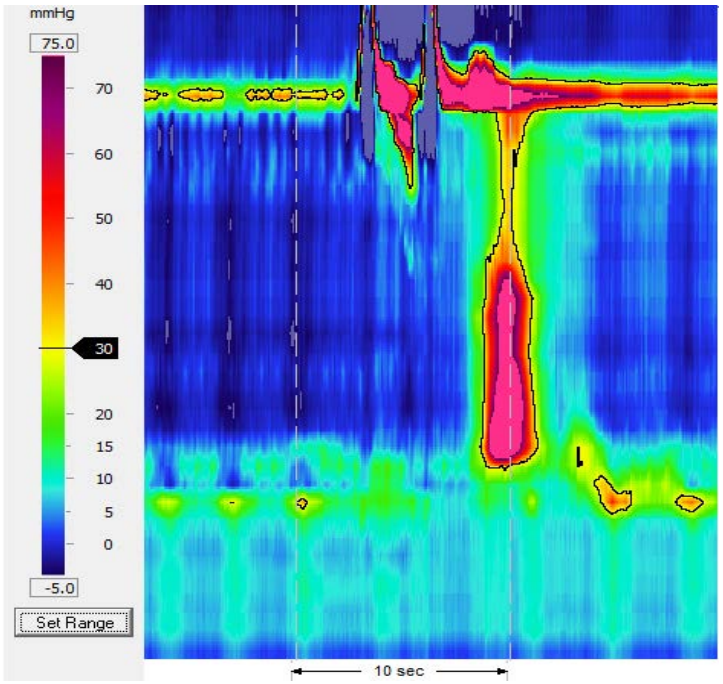


Figure 5.2 HRM of an ineffective solid swallow in a healthy subject. The first non-propagating pharyngeal swallow was quickly followed by an ineffective peristalsis (spasm). This was not associated with dysphagia, pain or discomfort. All other solid swallows that followed were normal. This is an example of how healthy subjects also can present with episodes of ineffective dysmotility, but in the absence of symptoms such events were considered to be of questionable significance.

HRM parameters and definitions

(Figure 5.1, 5.3 and 5.4)

Primary outcome measurements known to be associated with effective bolus transport were semi-automated; calculated automatically after the peristaltic markers and LOS pressure margins were manually repositioned:

- **Proximal transition zone (PTZ) length**; a parameter that reflects coordination between the proximal and distal contractile segments. The PTZ was defined as a separation between the proximal and mid-distal contraction front using a 30 mmHg isocontour.[36,125,243] (Figure 5.4)
- **PTZ nadir pressure**; this was calculated using a semi-automated function in the Manoview software (Smartmouse) which calculates the average pressure within any fixed area. The PTZ nadir pressure for every swallow was measured within the proximal and mid-distal 30 mmHg-derived contraction separation. (Figure 5.4) If no break occurred within 30 mmHg, the isobaric contour function was manually increased to the pressure at which a break appeared within the PTZ region and this was considered to be the PTZ nadir pressure.
- **Contractile Front Velocity (CFV)**; velocity of peristalsis of the distal contractile segment referenced to a 30 mmHg isobaric contour.[36,125]
- **Distal Contractile Integral (DCI)**; measure of contractile vigour of the distal contractile segmental. A parameter that integrates the length (cm), contractile pressure (mmHg) and duration (sec) of the distal contraction segment.[36,125]
- **Integrated Relaxation Pressure (IRP)**; a parameter that reports the lowest mean electronic Sleeve (e-Sleeve) pressure for four continuous or non-continuous seconds during OGJ relaxation.[134] This is a measure of compartmentalised pressure between the hiatal canal and the peristaltic wavelength (intra-bolus pressure; see below) which takes into account the mean gastric pressure for every swallow. It is really a measure of the bolus being forced through the OGJ and, can therefore gauge the obstruction of flow through the OGJ.

Secondary parameters needed to be measured manually using the 30 mmHg isocontour (Figure 5.4):

- **Peristaltic oesophageal length**; from the lower border of the upper oesophageal sphincter (UOS) to the upper border of the lower oesophageal sphincter (LOS).
- **Proximal contraction length**; from the lower border of the upper oesophageal sphincter to the start of PTZ
- **% proximal contraction length**; proximal contraction length corrected to the total oesophageal length:

  $$\frac{\textbf{Proximal oesophagus length}}{\textbf{Total oesophageal length}} \times 100$$

- **Distal contraction length**; from the end of the PTZ to the upper border of the LOS
- **% distal contraction length**; distal contraction length corrected to the total oesophageal length

  $$\frac{\textbf{Distal oesophagus length}}{\textbf{Total oesophageal length}} \times 100$$

- **Distal contraction wave duration**; the length of time required for a peristalsis contraction wave to pass down the distal oesophagus. (Figure 5.3)
- **Contractile pressure (Amplitude)**; measured at 3, 7 and 11 cm proximal to the upper border of the OGJ (these measurements were provided for direct comparison with conventional manometry metrics).
- **Intra-bolus Pressure (IBP)**; 3 second average of compartmentalised pressure below the peristaltic contraction and 1 cm above the OGJ. (Figure 5.3)

During the test meal, to standardise and facilitate comparison between water, bread and meals, a uniform 30 mmHg isobaric contour defined peristaltic integrity for all swallows.[36,125] Primary HRM parameters associated with successful bolus transport measured during the standardised test meal were:

- Integrated Relaxation Pressure (IRP) [134]
- Intra-bolus Pressure (IBP)
- Contractile Front Velocity (CFV) [36,125]
- Distal Contractile Integral (DCI)[36,125]
- Also breaks in the 30 mmHg pressure contour were recored[36,125,243,246]

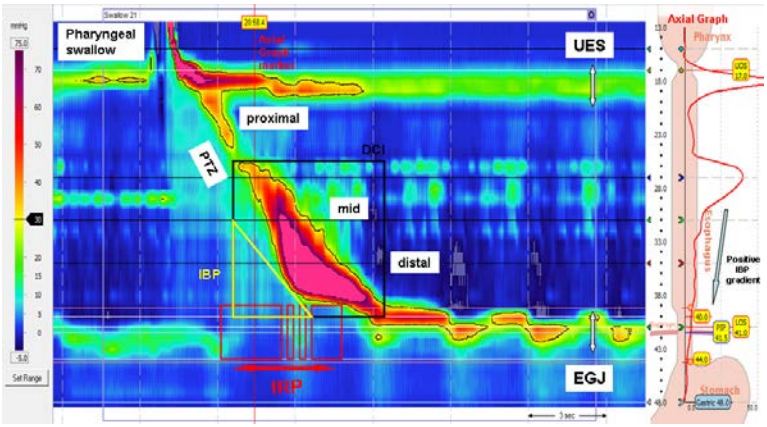


Figure 5.3 High Resolution Manometry of a normal swallow. Important landmarks and metrics essential for predicting bolus transport are highlighted. A 30 mmHg contour (black line circumscribing peristalsis) is superimposed on the image.
(UES: Upper oesophageal sphincter; PTZ Proximal transition zone; EGJ: Oesophago-gastric junction; IRP: Integrated relaxation pressure, IBP; Intra-bolus pressure, DCI; Distal Contractile Integral.)
(Reproduced from Sweis et al. NGM 2011.[276])

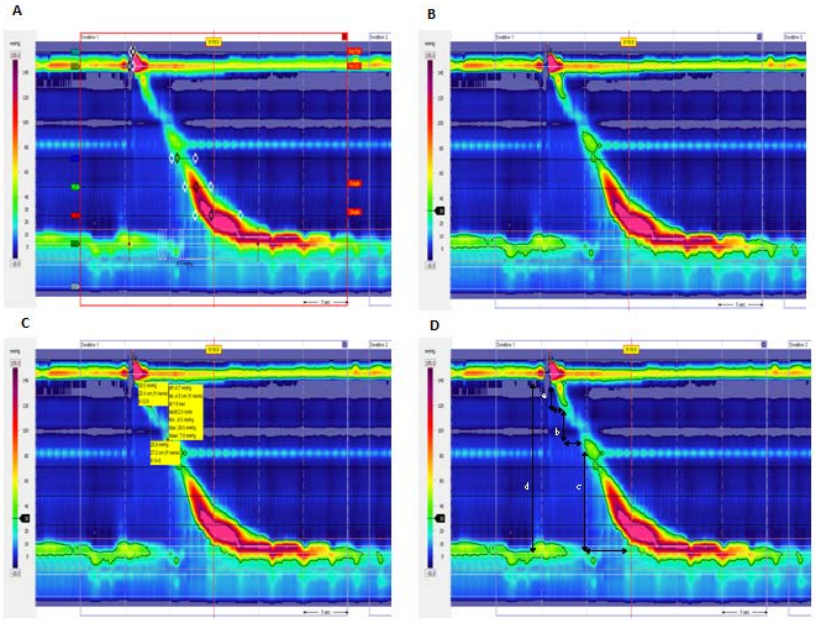


Figure 5.4 Proximal transition zone (PTZ) measurement technique. (A) After initial semi-automated analysis and manual re-positioning, (B) the isobaric contour was adjusted to 30 mmHg. (C) The PTZ nadir pressure (bordered by the 30 mmHg-derived proximal and distal peristaltic segments) was calculated using the Manoview 'smart-mouse' function. (D) Then the vertical length of the proximal (a) and distal (c) peristalsis segments as well as the PTZ (b) were measured with the 'smart-mouse' function and these were corrected to the total length of the oesophageal peristalsis (d).

Primary analysis assessed the association between dysmotility and symptoms; however apart from during the post-prandial observation period, as no healthy subject reported symptoms, symptom association will be covered in Chapter 6.

Multiple Water Swallow (MWS; Free drinking of 200 ml water)

Primary analysis:

A semi-quantitative assessment of oesophageal motor suppression and LOS outflow obstruction was made during MWS.[277] Primary parameters measured during the free drinking of 200ml water included:

- Total volume of water swallowed (without stopping)
- Total number of swallows required to complete the drink (without stopping)
- Total time required to complete the drink (without stopping)
- Presence/absence of oesophageal clearance contraction after MWS completion
- Presence/absence of an LOS after-contraction after MWS completion
- An un-validated score of the degree of obstruction to flow of water was rated: 0 - no contractions, 1 - almost complete contractions, 2 – partial contractions, 3 – minimal contractions, 4 - no suppression of contraction/complete obstruction.

Secondary MWS analysis measurements included:

- Number of swallows required to relax the LOS using the 15 mmHg isocontour + the % corrected to the total number of swallows required to complete the drink
- Time required to relax the LOS using the 15 mmHg isocontour + the % corrected to the total time required to complete the drink
- Oesophageal shortening measured as the difference in LOS position pre- and post-MWS. The pre-MWS resting LOS position was measured just prior to free drinking and the post-MWS position was measured at the initiation of the post-peristalsis after-contraction.
- LOS pressure difference from pre- to post-MWS. The LOS pressure was the mean pressure within a 1 cm area from the proximal to the distal LOS margins. The difference in LOS pressure was calculated as the difference in

pressure just prior to initiation of MWS and at the initiation of the post-peristalsis after-contraction.

- Volume per swallow was calculated as the total volume of water drunk divided by the total number of swallows required to finish the drink (without stopping)
- Volume of swallow required before LOS relaxation was calculated as the predicted volume of every swallow (see point above) multiplied by the total number of swallows required before LOS relaxation using the 15 mmHg isobaric contour.

Post meal observation period

During the ten minute observation period, transient lower oesophageal sphincter relaxations (TLOSRs), swallow-related lower oesophageal sphincter relaxations (SLOSRs) and other events associated with a common cavity (e.g. rumination) were recorded.

A TLOSR was defined according to standard criteria:[278]

1) absence of swallowing for 4 sec before and 2 sec after the onset of LOS relaxation (this differentiated a TLOSR from an SLOSR by the absence of a swallow during the preceding 4 seconds)
2) a common cavity with an abrupt rise of ≥5 mmHg in intra-oesophageal pressure
3) spontaneous fall in LOS pressure at a rate of ≥1 mmHg/s
4) time from onset to complete relaxation of ≤10sec

Finally, the frequency and time that the LOS gradually lost pressure (drift >10 sec) which was not associated with a common cavity was recorded. Supra-gastric belching was not assessed as concurrent impedance testing was not available.

5.2.4 Statistical methods

Comparing the oesophageal response documented on HRM and barium studies to physiologic challenge in 17 healthy volunteers, Fox et al[36] revealed an average increase of 20% and 10% in contractile pressures for the mid- and distal-oesophagus moving from the upright to the supine positions respectively. Similarly, comparing liquid and solid swallows revealed an increase of 28% and 16% in contractile pressures for the mid- and distal-oesophagus respectively. Therefore for the current study, recruitment of at least 20 volunteers was required.

Spatiotemporal plots of upright water and bread swallows were assessed by 3 investigators and supine swallows were assessed by 2 investigators. The Intra-class Correlation Coefficient (ICC) was used to interpret agreement for manually derived parameters corrected for chance. An ICC of <0.2 implies little, >0.5 good and >0.80 almost perfect agreement.[279] The study protocol was lengthy and the analysis (if completed in detail) was time consuming. Therefore results from a random subset of 12 healthy volunteers were analysed and rated by the assessors following a brief period of training.

Mann-Witney and Wilcoxon tests were used for nonparametric comparisons of quantitative swallows. $P<0.05$ was considered statistically significant. Friedman test was used for analysis of variance for multiple comparisons of nonparametric data within groups (i.e. comparing water, bread and test meal parameters within the same patient group). Results were reported as Median (Inter-quartile range; IQR) and Mean ± Standard Error (Standard Deviation). Normative data was presented with 5^{th} and 95^{th} percentiles. Pearson's coefficient (PC) assessed the strength of relationship between the frequency of effective swallows and the total time required to consume meals.

5.3 Results

5.3.1 Single bolus swallows

Participants

Manometry was well tolerated and technically adequate swallows were successfully acquired in the upright and supine positions for liquid (23 subjects) and solid (21 subjects) swallows. A median of 5 liquid and 4 solid swallows were available for analysis in each position. (UL = Upright liquid; US = Upright solid; SL = Supine liquid; SS = Supine solid). The overall number of swallows and peristaltic success for every bolus consistency and body position are described in Table 5.1.

The distal oesophageal contractile response showed an increased number of simultaneous (spasm) and failed contractions for solid than liquid swallows in the upright (LU 13.9% vs. SU 32.1%; p=0.004) and supine (LS 7.6% vs. SS 23.0%; p=0.039) positions. On the other hand there was no difference in the frequency of nonperistaltic swallows with shift in position of the same consistency (LU 13.9% vs. LS 7.6%; p=0.550 and SU 32.1% vs. SS 23.0%; p=0.276). (Table 5.1)

Swallowing behaviour with liquid and solid bolus during the HRM study

A median (range) of 1 (1,1) and 1 (1,3) pharyngeal swallows were required to swallow liquid and solid bolus respectively. 11/21 participants required 2 pharyngeal swallows and 1 subject required 3 swallows on at least one occasion to clear the pharynx of bread prior to the appearance of a distal oesophageal contraction. There was no difference in the key parameters which describe the distal oesophageal contraction (PTZ length, CFV, DCI) following multiple compared to single pharyngeal deglutitions (p = NS for all).

Functional anatomy of the oesophagus

Oesophageal peristalsis (Figure 5.4 and 5.5; Table 5.2 – 5.4)

Overall oesophageal length was not altered by change in consistency (Liquid 21.8 (20.6,24.3) cm vs. Solid 22.5 (20.5, 23.9) cm; p=0.537). Proximal Transition Zone (PTZ) length was smaller for solid than liquid swallows and in the upright (LU vs. SU p<0.001) and supine (LS vs. SS p=0.002) positions. These remained significant when corrected for total oesophageal length (LU vs. SU p<0.001 and LS vs. SS p=0.002). PTZ length was also smaller when moving from the upright to supine positions for liquids (LU vs. LS p=0.002) but not solids (SU vs. SS p=0.08); however these were both significant when corrected for total oesophageal length (LU vs. LS p=0.002 and SU vs. SS p=0.023). (Table 5.3, Figure 5.4). Similarly PTZ mean pressure was higher for solids than liquids in upright (LU vs. SU p=0.001) and supine (LS vs. SS p<0.001) positions as well as in the supine than upright position for liquids (LU vs. LS p=0.042) and solids (SU vs. SS p=0.005).

The proximal contractile segment (proximal to the PTZ) was not affected by changes in bolus consistency in upright (LU vs. SU p=0.560) and supine (LS vs. SS p=0.079) positions nor with change in position during liquid (LU vs. LS p=0.094) and solid (SU vs. SS p=0.926) swallows. These parameters remained non-significant when corrected for oesophageal length (LU vs. SU p=0.073; LS vs. SS p=0.085, LU vs. LS p=0.159 and SU vs. SS p=0.835 respectively). On the other hand, the distal contractile segment increased in length for solid compared to liquid swallows in the upright (LU vs. SU p=0.004) and supine (LS vs. SS p=0.016) positions, and on moving from the upright to the supine position for liquids (LU vs. LS p<0.001) and solids (SU vs. SS p=0.013). However when corrected for oesophageal length, distal oesophageal length did not change for solids when moving from upright to supine position (LU vs. SU p=0.002, LS vs. SS p=0.014, LU vs. LS p=0.001 and SU vs. SS p=0.099). (Table 5.3 and 5.4)

Results for the primary parameters describing oesophageal function are presented in Table 5.2. Representative changes in oesophageal function and PTZ are illustrated in Figure 5.5.

	Upright liquid	Total n=115	Upright solid	Total n=78	Supine liquid	Total n=105	Supine solid	Total n=74
Peristaltic	86.1%	99	67.9%	53	92.4%	97	77.0%	57
Non-peristaltic	13.9%	16	32.1%	25	7.6%	12	23.0%	17
Ineffective	4.3%	5	14.1%	11	7.6%	8	6.8%	5
Failed	9.6%	11	17.9%	14	3.8%	4	16.2%	12

Table 5.1 Oesophageal response to liquid and solid bolus in upright and supine positions. Peristaltic swallows were more frequent for liquids than solids in both the upright and supine positions

	LIQUID UPRIGHT					SOLID UPRIGHT				
	Median (IQR)	5th %ile	95th %ile	Mean±SE (SD)	CV	Median	5th %ile	95th %ile	Mean±SE (SD)	CV
Integrated relaxation pressure (mm Hg)	5.9 (3.2,7.0)	1.1	15.8	6.2±0.9 (4.3)	70%	8.4 (5.9,12.3)	1.9	21.4	9.7±1.3 (5.9)	61%
Proximal transition zone length (cm)	3.2 (1.9,7.4)	0.7	10.9	4.7±0.7 (3.4)	73%	0.5 (0.0,2.5)	0.0	6.8	2.1±0.7 (3.0)	146%
Contractile front velocity (cm/s)	3.6 (3.1,4.4)	2.6	5.5	4.1±0.5 (2.2)	54%	3.2 (2.4,3.4)	2.0	4.4	3.2±0.2 (0.9)	28%
Distal contractile integral (mmHg-cm-s)	734.4 (478.3,1366.0)	180.7	2444.0	1058.7±198.0 (949.6)	90%	1116.6 (607.3,2104.9)	404.6	5845.6	1892.6±397.1 (1819.7)	96%

	LIQUID SUPINE					SOLID SUPINE				
	Median	5th %ile	95th %ile	Mean±SE (SD)	CV	Median	5th %ile	95th %ile	Mean±SE (SD)	CV
Integrated relaxation pressure (mm Hg)	3.3 (1.7,5.3)	-0.4	8.7	3.8±0.6 (2.9)	76%	5.9 (3.7,9.7)	1.2	12.8	6.5±0.9 (4.3)	67%
Proximal transition zone length (cm)	2.9 (1.1,4.5)	0.5	6.5	3.0±0.5 (2.3)	78%	0.0 (0.0,2.3)	0.0	5.0	1.4±0.5 (2.2)	164%
Contractile front velocity (cm/s)	3.3 (3.0,3.5)	2.3	4.8	3.4±0.2 (1.0)	29%	3.2 (2.4,3.5)	1.8	4.4	3.2±0.3 (1.3)	40%
Distal contractile integral (mmHg-cm-s)	944.9 (522.9,1421.1)	196.8	2433.4	1303.4±341.1 (1636.0)	126%	1636.7 (750.5,2814.8)	330.4	4040.9	2225.4±611.4 (2801.9)	126%

Table 5.2 HRM normal values for primary parameters describing oesophageal function for liquid and solid bolus swallows in the upright and supine positions. (CV = Coefficient of variation)

Oesophageal segment (normalized to total length (%))	Upright Liquid Median (IQR)	Upright Solid Median (IQR)	Supine Liquid Median (IQR)	Supine Solid Median (IQR)
Proximal length	24.5% (15.0,27.4%)	24.4% (20.9,34.2%)	23.4% (18.4,28.7%)	25.6% (22.8,30.0%)
PTZ length	15.2% (8.7,30.7%)	3.5% (0.0,11.8%)	10.8% (4.7,16.2%)	0.0% (0.0,6.3%)
Distal length	59.0% (46.4,66.0%)	65.0% (57.7,71.5%)	66.2% (57.9,70.5%)	68.9% (61.4,74.7%)

Table 5.3 PTZ parameters corrected for oesophageal length.

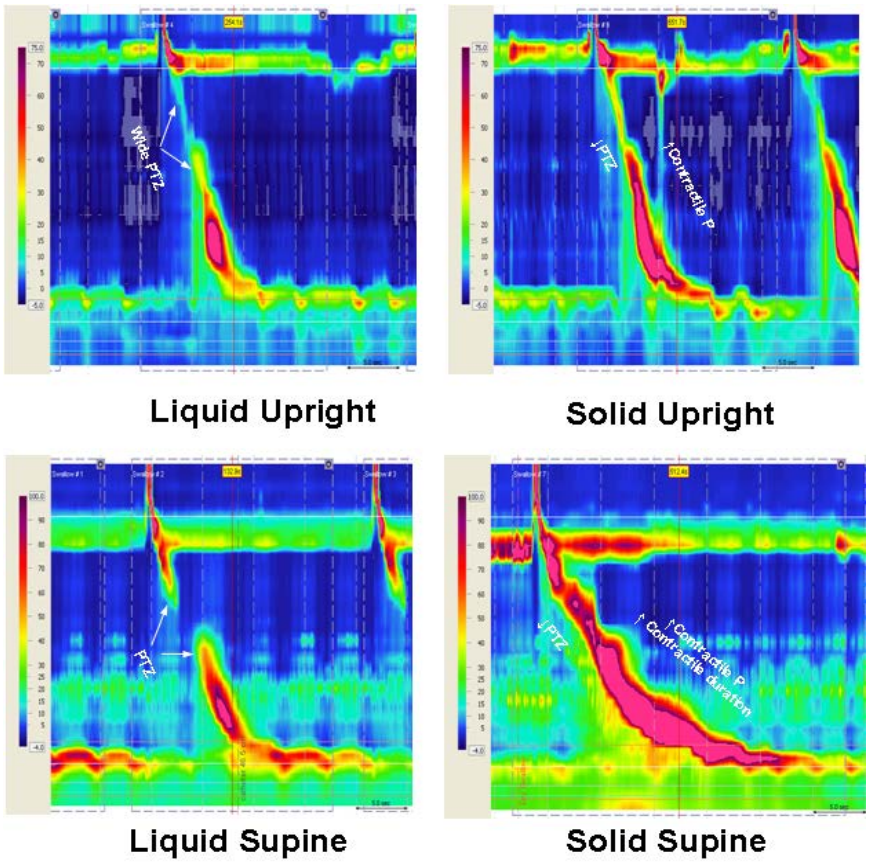


Figure 5.5 Liquid and solid bolus swallows in the upright and supine positions. Note the improvement in coordination between proximal and mid-distal contraction waves and the increase in contractile vigour that occurs with movement from upright to supine position and with solid bolus consistency.

	LIQUID UPRIGHT					SOLID UPRIGHT				
	Median (IQR)	5th %ile	95th %ile	Mean±SE (SD)	CV	Median (IQR)	5th %ile	95th %ile	Mean±SE (SD)	CV
Peristaltic coordination (PTZ, functional anatomy)										
PTZ mean pressure @ 30mmHg (mmHg)	12.3 (8.3,17.9)	5.0	24.9	13.6±1.5 (7.2)	53%	20.3 (12.9,29.5)	10.3	49.0	24.3±3.0 (13.9)	57%
PTZ time @ 30mmHg (s)	2 (1,2)	1	4	2±0 (1)	55%	1 (0,1)	0	3	1±0 (1)	119%
Proximal contractile segment @ 30mmHg (cm)	5.0 (3.6,6.1)	2.6	6.9	4.9±0.4 (1.8)	37%	5.4 (4.5,7.3)	3.7	8.5	5.9±0.4 (1.9)	31%
Distal contractile segment @ 30mmHg (cm)	12.8 (11.1,14.5)	8.6	18.0	12.8±0.6 (2.9)	23%	14.5 (12.4,15.5)	10.0	18.7	14.3±0.6 (2.9)	21%
Peristaltic velocity										
Onset velocity (between 11.0 & 3.0 above LES) (cm/s)	3.5 (3.3,4.2)	2.5	6.1	3.9±0.2 (1.1)	27%	3.5 (2.7,4.0)	2.1	6.3	3.7±0.3 (1.4)	37%
Onset velocity (between 7.0 & 3.0 above LES) (cm/s)	4.1 (3.5,5.5)	2.6	9.2	4.9±0.5 (2.5)	51%	3.7 (2.5,4.0)	1.9	6.0	4.0±0.6 (2.8)	70%
Contractile front velocity (cm/s)	3.6 (3.1,4.4)	2.6	5.5	4.1±0.5 (2.2)	54%	3.2 (2.4,3.4)	2.0	4.4	3.2±0.2 (0.9)	28%
Peristaltic Vigour (Contractile pressure, DCI)										
Wave amplitude (mean, 3.0 & 7.0 above LES) (mm Hg)	57.4 (53.3,97.8)	35.8	137.1	75.0±7.2 (34.6)	46%	74.6 (63.8,122.4)	45.6	153.5	88.4±8.3 (38.2)	43%
Wave amplitude (@11.0 above LES) (mm Hg)	39.3 (30.5,64.3)	22.2	84.0	46.8±4.6 (22.0)	47%	51.1 (42.2,71.5)	20.1	116.0	59.9±6.6 (30.2)	50%
Wave duration (mean at 3.0 & 7.0 above LES) (sec)	3.0 (2.8,3.4)	2.5	4.2	3.1±0.1 (0.5)	17%	3.5 (2.9,4.2)	2.3	5.5	3.6±0.2 (1.0)	28%
Distal contractile integral (mmHg cm·s·)	734.4 (478.3,1366.0)	180.7	2444.0	1058.7±198.0 (949.6)	90%	1116.6 (607.3,2104.9)	404.6	5845.6	1892.6±397.1 (1819.7)	96%
Intra-bolus Pressure										
Intrabolus pressure (mmHg)	8.9 (6.7,13.8)	0.9	17.2	9.8±1.1 (5.4)	56%	13.0 (10.9,21.0)	4.8	25.7	14.7±1.5 (6.9)	47%

	LIQUID SUPINE					SOLID SUPINE				
	Median (IQR)	5th %ile	95th %ile	Mean±SE (SD)	CV	Median (IQR)	5th %ile	95th %ile	Mean±SE (SD)	CV
Peristaltic coordination (PTZ, functional anatomy)										
PTZ mean pressure @ 30mmHg (mmHg)	15.1 (10.9,25.1)	6.0	45.4	18.9±2.6 (12.3)	65%	34.0 19.1,51.3)	11.5	58.0	35.0±4.1 (18.7)	53%
PTZ time @ 30mmHg (s)	1 (1,2)	0	2	1±0 (1)	60%	0 (0,1)	0	2	1±0 (1)	134%
Proximal contractile segment @ 30mmHg (cm)	5.3 (4.1,6.7)	3.0	7.3	5.2±0.4 (1.8)	35%	5.7 (5.2,6.4)	3.4	7.5	5.8±0.3 (1.4)	24%
Distal contractile segment @ 30mmHg (cm)	14.7 (13.1,16.0)	11.3	18.1	14.6±0.5 (2.5)	17%	14.9 (14.1,16.9)	12.9	20.7	15.6±0.6 (2.6)	16%
Peristaltic velocity										
Onset velocity (between 11.0 & 3.0 above LES) (cm/s)	3.5 (3.3,4.0)	2.2	5.9	3.7±0.2 (1.1)	29%	3.2 (2.7,3.7)	1.9	4.7	3.3±0.2 (1.1)	33%
Onset velocity (between 7.0 & 3.0 above LES) (cm/s)	3.8 (3.2,4.9)	2.6	7.7	4.4±0.4 (2.2)	49%	3.7 (2.4,3.9)	2.0	5.3	3.6±0.3 (1.6)	44%
Contractile front velocity (cm/s)	3.3 (3.0,3.5)	2.3	4.8	3.4±0.2 (1.0)	29%	3.2 (2.4,3.5)	1.8	4.4	3.2±0.3 (1.3)	40%
Peristaltic Vigour (Contractile pressure, DCI)										
Wave amplitude (mean, 3.0 & 7.0 above LES) (mm Hg)	72.5 (56.0,91.2)	31.5	148.4	79.8±8.2 (39.3)	49%	90.5 (62.5,116.2)	41.4	188.2	99.5±12.1 (55.6)	56%
Wave amplitude (@11.0 above LES) (mm Hg)	52.0 (38.8,70.6)	23.3	102.1	57.5±6.2 (29.8)	52%	63.9 (42.6,84.6)	31.1	134.0	70.2±7.3 (33.5)	48%
Wave duration (mean at 3.0 & 7.0 above LES) (sec)	3.2 (2.6,3.3)	2.1	4.1	3.1±0.2 (0.8)	24%	3.3 (3.1,4.5)	2.8	5.3	3.9±0.3 (1.4)	35%
Distal contractile integral (mmHg cm·s·)	944.9 (522.9,1421.1)	196.8	2433.4	1303.4±341.1 (1636.0)	126 %	1636.7 (750.5,2814.8)	330.4	4040.9	2225.4±611.4 (2801.9)	126%
Intra-bolus Pressure										
Intrabolus pressure (avg max,mmHg)	7.9 (5.3,12.2)	1.8	16.0	8.4±1.0 (4.8)	57%	10.7 (9.1,16.2)	3.9	19.9	12.6±1.2 (5.5)	44%

Table 5.4 HRM parameters defining the functional anatomy of the oesophagus. (PTZ = Proximal transition zone break in contractile pressure front; CV = Coefficient of variation)

Lower Oesophageal Sphincter

The median (IQR) LOS basal pressure was 22.9 (13.7,27.0) mmHg in the upright and 18.9 (12.8,26.4) mmHg in the supine position (p=0.516). The median (IQR) LOS total length was 3.2 (3.0,3.6) cm and the intra-abdominal length was 2.0 (1.5,2.6) cm. This did not change between liquid and solid swallows in the upright (LU vs. SU total p=0.680 and intra-abdominal p=0.459 LOS length) or supine (LS vs. SS total p=0.513 and intra-abdominal p=0.566 LOS length) position respectively. (Table 5.5) No healthy subject had a hiatus hernia at baseline.

	LIQUID UPRIGHT					SOLID UPRIGHT			
	Median (IQR)	5th %ile	95th %ile	Mean±SE (SD)	CV	Median	5th %ile	95th %ile	Mean±SE (SD)
LOS basal pressure	22.9 (13.7,27.0)	7.9	33.9	21.3±2.0 (9.4)	44%				
LOS Length	3.2 (3.0,3.6)	2.6	4.0	3.3±0.1 (0.5)	15%	3.2 (3.0,3.5)	2.8	3.8	3.2±0.1 (0.4)
Intra-abdominal LOS	2 (1.5,2.6)	0.4	3.1	2.0±0.2 (0.9)	45%	2 (1.5,2.6)	0.5	3.0	2.0±0.2 (0.7)
	LIQUID SUPINE					SOLID SUPINE			
	Median	5th %ile	95th %ile	Mean±SE (SD)	CV	Median	5th %ile	95th %ile	Mean±SE (SD)
LOS basal pressure	18.9 (12.8,26.4)	8.2	38.4	20.2±2.3 (11.1)	55%				
LOS Length	3.0 (2.8,3.4)	2.6	4.1	3.2±0.1 (0.5)	17%	3.2 (2.9,3.5)	2.5	4.2	3.2±0.1 (0.5)
Intra-abdominal LOS	1.9 (1.6,2.2)	1.1	2.6	1.9±0.1 (0.5)	28%	1.9 (1.5,2.3)	1.0	2.8	1.9±0.1 (0.6)

Table 5.5 Lower oesophageal sphincter (LOS) measurements. Upright and supine basal pressure, total and intra-abdominal length for liquid and solid swallows.

Baseline LOS pressure was the same for liquid and solid swallows. Total and intra-abdominal length was measured separately for every swallow.

Integrated Relaxation Pressure (IRP) and Intra-Bolus Pressure (IBP)

IRP was higher for solids than liquids in both positions (LU vs. SU and LS vs. SS; p<0.001 for both). At the same time IRP was higher in the upright than the supine position for both bolus consistencies (LU vs. LS p=0.002, SU vs. SS p=0.004) (Table 5.2, Figure 5.6)

Similarly IBP was higher for solids than liquids in both positions (LU vs. SU and LS vs. SS; p<0.001 for both) as well as in the upright than the supine position for both bolus consistencies (LU vs. LS p=0.029, SU vs. SS p=0.006) (Table 5.4, Figure 5.7)

Peristaltic velocity

There was a significant decrease in contractile front velocity (CFV) for solid compared to liquid swallows in the upright position (LU vs. SU p=0.01). This decrease in CFV did not reach significance in the supine position (LS vs. SS p=0.186). Also no effect on CFV was observed for position change for liquids and solids respectively (LU vs. LS p=0.118, SU vs. SS p=0.663). (Table 5.2, Figure 5.8).

Contractile vigour

Contractile vigour (DCI), was greater for solid than liquid swallows in the upright (LU vs. SU p<0.001) and supine (LS vs. SS p=0.001) positions. All parameters increased also with change from the upright to the supine positions although these effects were not significant (LU vs. LS p=0.287 and SU vs. SS p=0.543). (Table 5.2, Figure 5.9)

These trends were consistent also for point measurements of contractility. Proximal to the LOS, contractility was higher for solid than liquid bolus in upright (LU vs. SU p<0.031) and supine (LS vs. SS p<0.001) positions. Although all parameters increased with change from upright to supine positions these did not achieve statistical significance (LU vs. LS p=0.689 and SU vs. SS p=0.107). (Table 5.4, Figure 5.10)

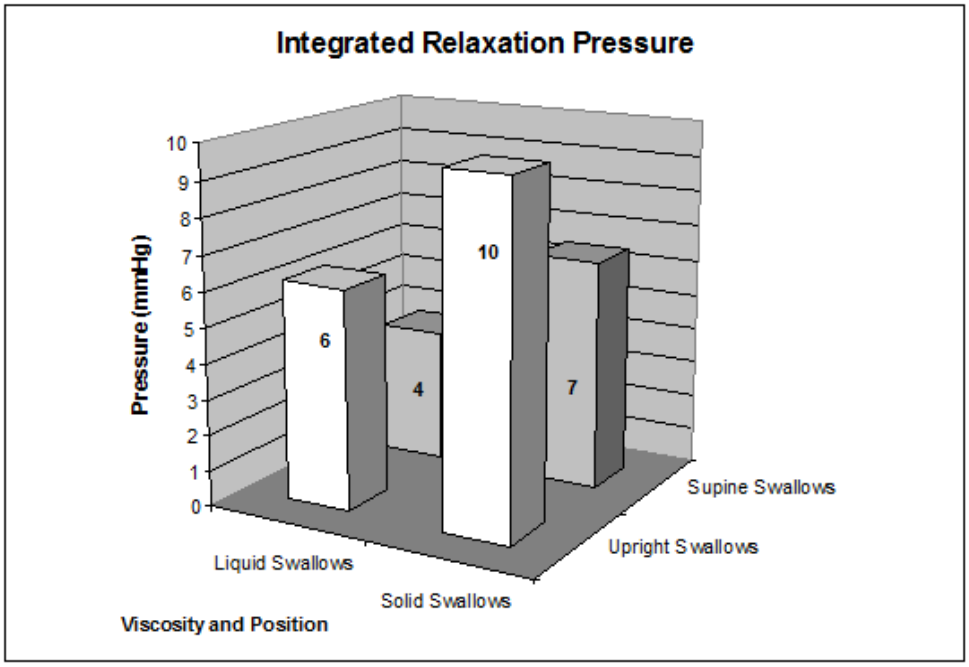


Figure 5.6 Effects of position change and bolus consistency on mean Integrated Relaxation Pressure.

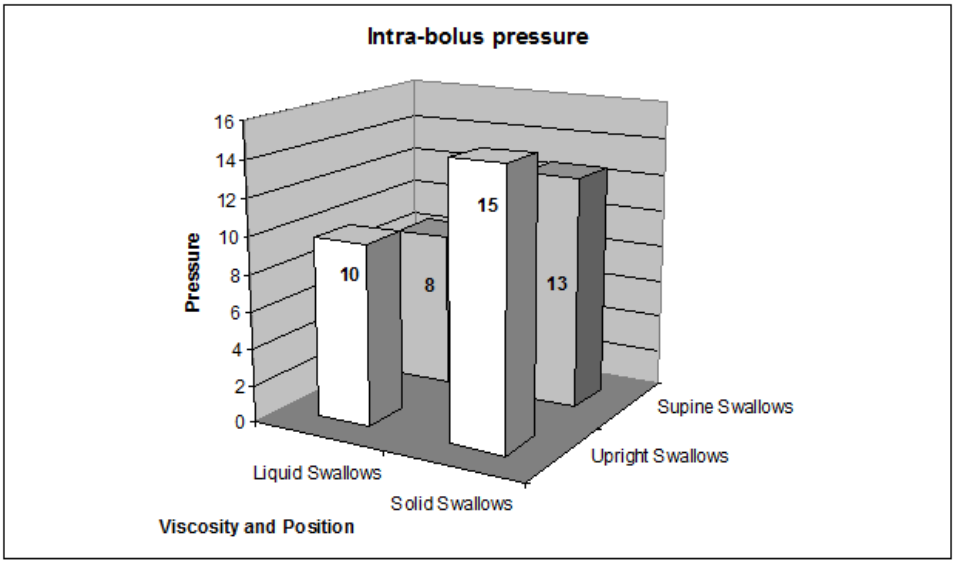


Figure 5.7 Effects of position change and bolus consistency on mean Intra-bolus Pressure.

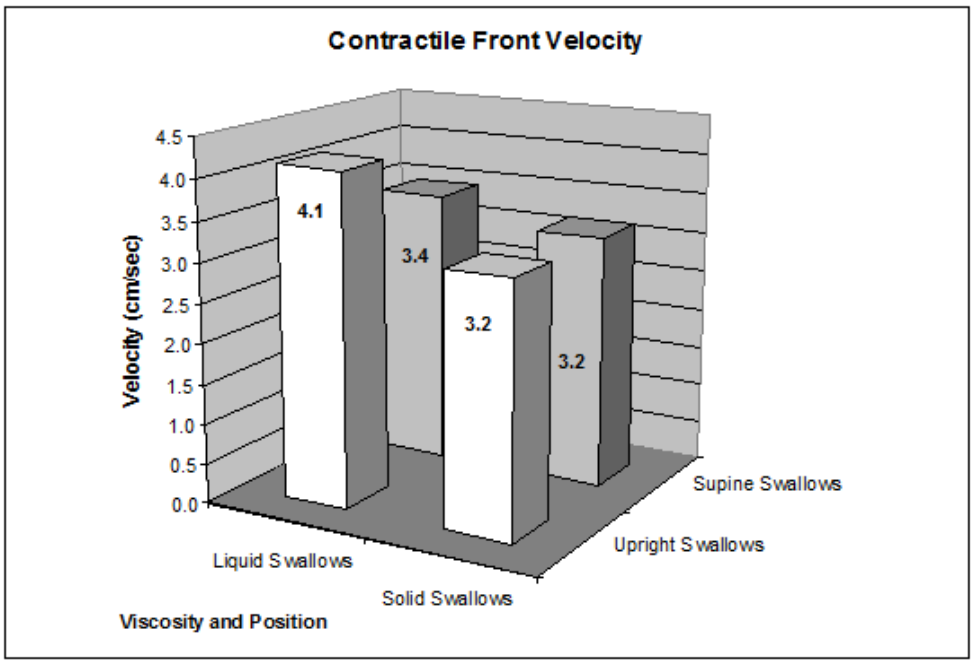


Figure 5.8 Effects of position change and bolus consistency on mean Contraction Front Velocity.

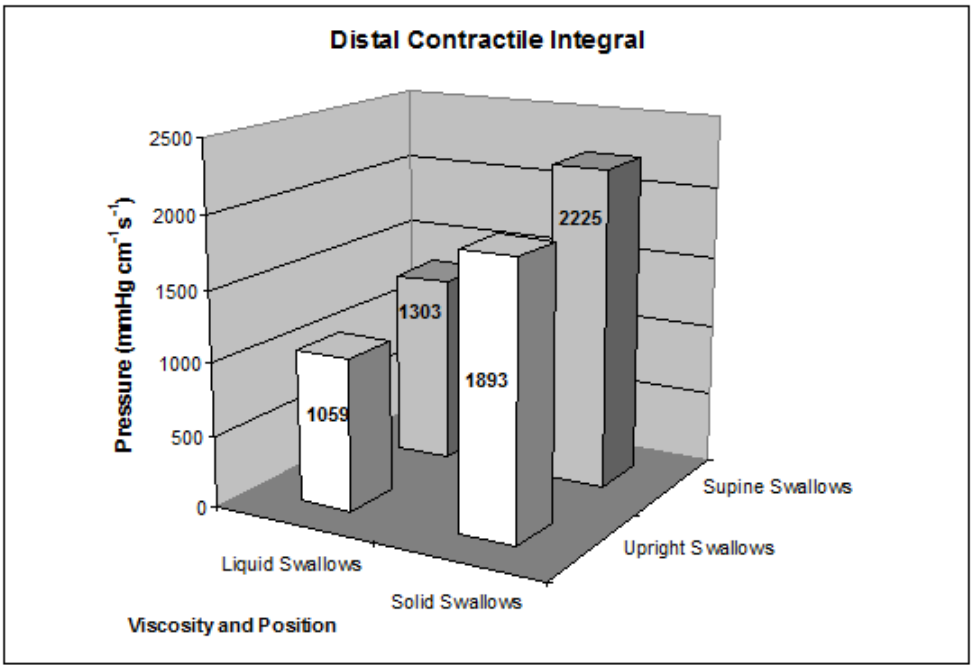


Figure 5.9 Effects of position change and bolus consistency on mean Distal Contractile Integral.

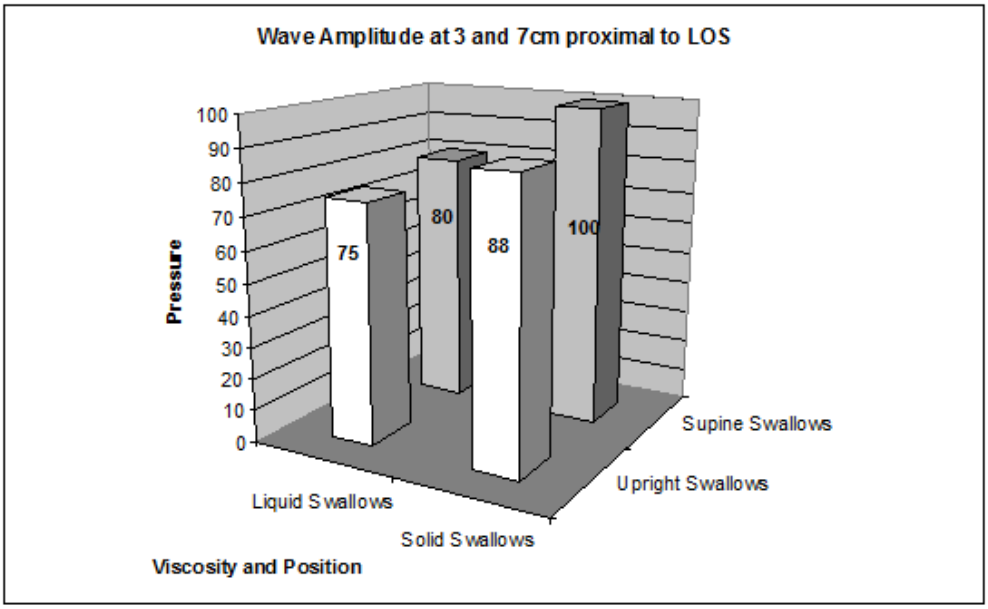


Figure 5.10 Effects of position change and bolus consistency on mean contractility at 3 and 7 cm proximal to the LOS

Inter-observer agreement

For parameters derived manually from spatiotemporal plots in the upright and supine position, the Intra-class Correlation Coefficient (ICC) between 3 assessors was >0.5 for all parameters measured using liquid and solid swallows. This implies very good agreement. The only exception was for velocity which was non-significant for both liquid and solid swallows only in the upright position. (Table 5.6)

	IRP	PTZ length @30mmHg	Velocity	Distal Wave Amplitude	IBP
3 raters					
Liquid Upright					
ICC	0.914	0.651	0.143	0.963	0.283
p=	<0.001	<0.001	0.214	<0.001	0.006
Solid Upright					
ICC	0.524	0.868	0.078	0.918	0.685
p=	0.002	<0.001	0.309	<0.001	<0.001
2 raters					
Liquid Supine					
ICC	0.951	0.897	0.766	0.981	0.848
p=	<0.001	<0.001	0.001	<0.001	<0.001
Solid Supine					
ICC	0.959	0.958	0.761	0.972	0.861
p=	<0.001	<0.001	0.001	<0.001	<0.001

Table 5.6 Inter-observer agreement. Intra-class Correlation Coefficient (ICC) between single liquid and solid bolus swallows for manually derived parameters in the upright and supine positions.

ICC <0.2 = little, >0.5 = good, >0.80 = excellent agreement

5.3.2 Test meal, Multiple water swallows and post-prandial observation

Participants

Manometry was tolerated and technically adequate swallows were acquired for 5 ml water, 1 cc bread and test meal for all 10 of the 23 healthy participants who agreed to carry on with the study protocol. This also included free drinking of 200 ml water (MWS) and a post-prandial observation period. The 13 who did not consent expressed concern at having a catheter in situ for longer periods and preferred to complete only the standard protocol of 5 ml water and 1 cc bread. No healthy subject was found to have a major motility disorder during the standard 5 ml water swallows (i.e. aperistalsis, oesophageal spasm, achalasia).

Water, bread and meal swallows in health: Motility and Function

(Table 5.7 and Figure 5.11)

There was a significant improvement in co-ordination (shorter median PTZ length and increased median pressure) during the test meal (0.7 cm and 42 mmHg) compared to water (3.2 cm and 13.7 mmHg) and bread (2.3 cm and 26.3 mmHg) swallows (Friedman p=0.004 and p=0.002 respectively). There was also an increase in the median contractile vigour (DCI) of the distal oesophageal segment during the test meal (1735.0 mmHg cm^{-1} s^{-1}) compared to water (919.2 mmHg cm^{-1} s^{-1}) and bread (934.0 mmHg cm^{-1} s^{-1}) swallows (Friedman p=0.001). There was no difference in IRP between the meal study, single water (p=0.262) or bread (p=0.208) swallows. On the other hand, there was a steady increase in the overall median IBP from water (6.8 mmHg; p=0.005), to bread (12.0 mmHg; p=0.017) and the test meal (19.4 mmHg; Friedman p=0.001). CFV was more rapid during water (3.7 cm/s; p=0.005) and bread (3.2 cm/s; p= 0.012) swallows than the test meal (2.1 cm/s; Friedman p=0.002).

Lower oesophageal sphincter (LOS)

LOS baseline studies were performed once at the start of the test after the patient acclimatised to the presence of the catheter (see Methods Chapter 2). LOS baseline pressure (19.0 (11.8, 27.7) mmHg), total LOS length (3.2 (2.9,3.2) cm) and intra-abdominal LOS length (2.3 (1.6,2.7) cm) were in keeping with normal published values.[247]

	5ml WATER SWALLOW		1cc BREAD SWALLOW		STANDARDISED MEAL						
	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	Median	5th %ile	95th %ile	Mean±SE (SD)	p (water vs meal)	p (bread vs meal)	p Friedman
IRP (mmHg)	5.0 (3.1,6.4)	5.5±1.4 (4.4)	7.6 (5.7,11.7)	9.2±1.9 (6.0)	6.1 (4.8,8.5)	4.2	10.7	6.8±0.8 (2.6)	0.262	0.208	0.021
IBP (mmHg)	6.8 (2.9,10.4)	6.7±1.5 (4.8)	12.0 (6.9,15.0)	12.1±2.0 (6.4)	19.4 (17.1,21.8)	11.0	27.6	19.4±1.8 (5.8)	0.005	0.017	0.001
PTZ break P (mmHg)	13.7 (9.4,16.4)	13.9±2.1 (6.5)	26.3 (18.9,31.2)	23.7±3.1 (9.7)	42.0 (39.1,46.1)	25.0	50.0	40.6±3.0 (9.5)	0.005	0.025	0.002
PTZ length (cm)	3.2 (2.1,6.6)	4.4±0.9 (2.8)	2.3 (0.7,2.6)	2.2±0.7 (2.1)	0.7 (0.4,1)	0.2	2.9	1.0±0.4 (1.2)	0.008	0.091	0.004
CFV (cm/s)	3.7 (2.9,4.8)	3.8±0.3 (1.1)	3.2 (3.0,3.6)	3.4±0.2 (0.6)	2.1 (2.0,2.3)	0.7	2.5	1.9±0.2 (0.7)	0.005	0.012	0.002
DCI (mmHg $cm^{-1}s^{-1}$)	919.2 (505.4,1394.5)	982.6±230.9 (730.2)	934.0 (557.5,1749.8)	1132.0±221.1 (699.0)	1735.0 (1322.9,2830.7)	765.6	4737.0	2204.5±486 (1536.8)	0.005	0.012	0.001

Table 5.7 Key parameters describing oesophageal motility and function in healthy subjects during water swallows, bread swallows and the test meal (n=10). P values are presented using Wilcoxon analysis (between water, bread and test meal) and Friedman analysis (overall change between modalities).

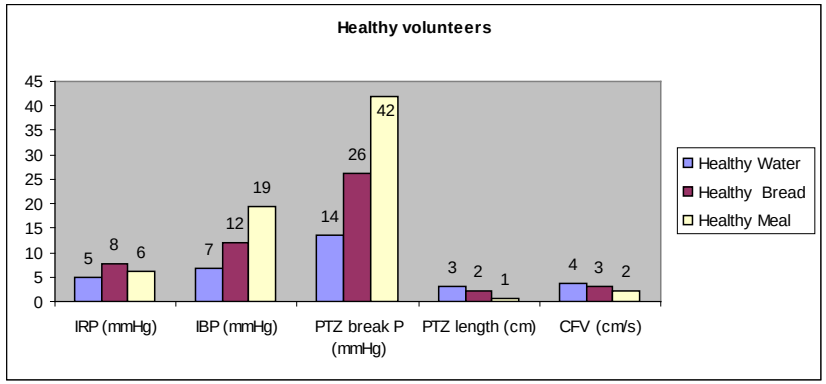


Figure 5.11a

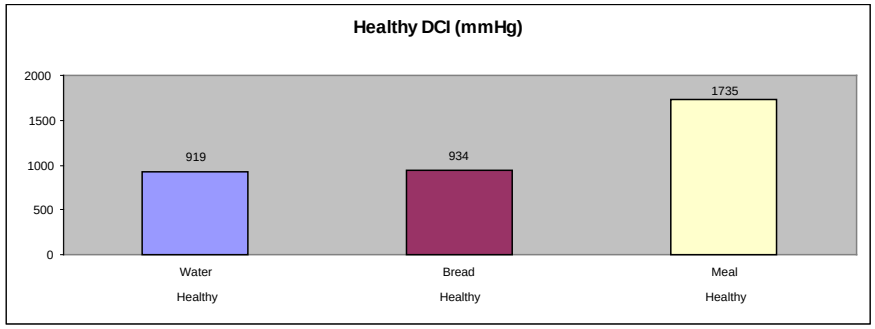


Figure 5.11b

Figure 5.11 Effect of changing bolus consistency (water, bread, meal) on primary parameters known to affect bolus transport. (n=10) Results are presented as median values. Note: Please refer to Table 5.7 for measurements of significance.

Swallow effectiveness for standardised meal

The median consumption time for the standardised meal was 399 (range 307-550) seconds and a median (IQR) of 29 (27,32) pharyngeal swallows were required to complete the meal. Of a total of 325 swallows, 167 (51.4%) were observed to be effective while 158 (48.6%) were non-peristaltic; 52 (16%) were ineffective (spasm or break in contractility ≥3cm) and 106 (32.6%) failed (<3 cm contraction). There was no correlation between the number of effective swallows and the time required to consume the meal (PC 0.351 p=0.320). (Figure 5.12) A representative HRM plot of swallows during a standardised test meal is shown in Figure 5.13.

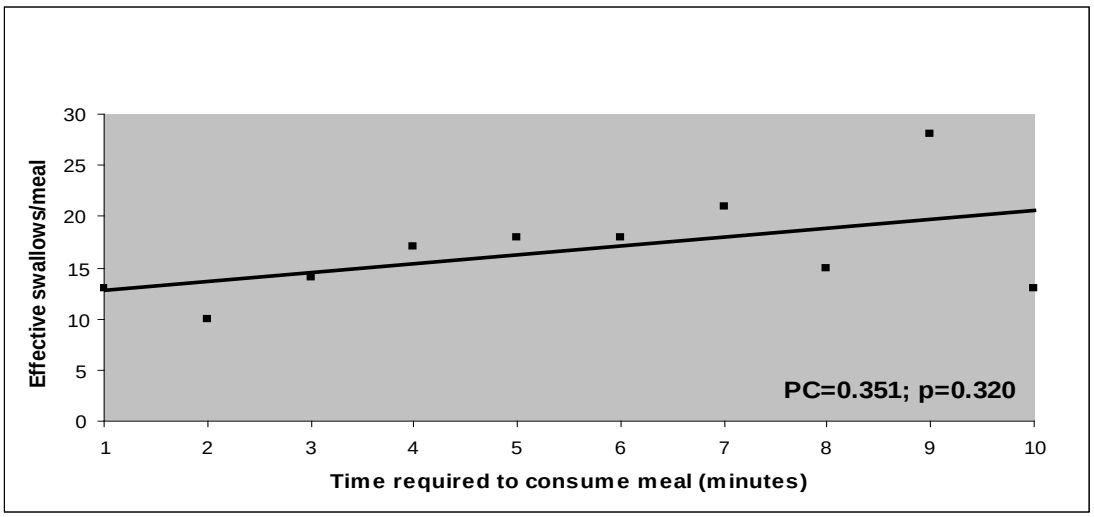


Figure 5.12 Frequency of effective swallows required to consume the meal over time in 10 healthy subjects.
(PC = Pearson's correlation)

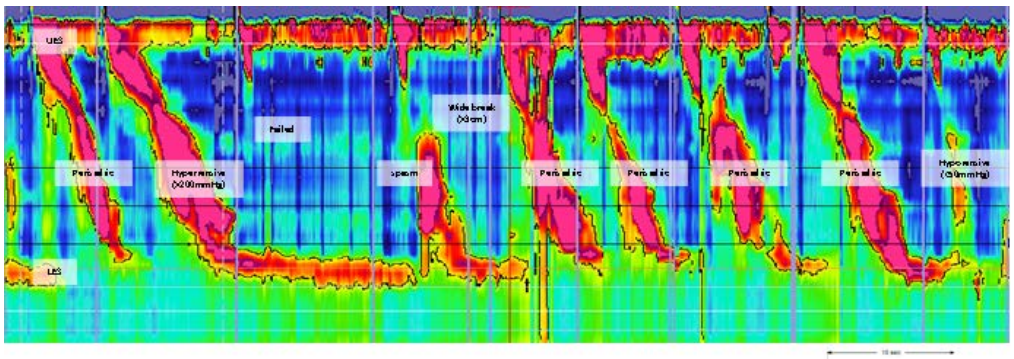


Figure 5.13 Frequency of effective swallows during a standardised test meal in a healthy volunteer. Labels are assigned to define the character of every pharyngeal/oesophageal deglutition.

Multiple water swallows (MWS) in health

A median (IQR) of 15.5 (11.8, 20.3) swallows were required to drink 200 ml water over a period of 22 (19, 29) seconds. (Table 5.8) A median (IQR) of 2 (0,3) swallows were required to open the LOS during free drinking. It was calculated that each swallow comprised a median of 13.5 ml, and an average of 25.6 ml (out of 200 ml) of water needed to be swallowed to achieve LOS opening at 15 mmHg. Furthermore, the oesophagus shortened by 0.3 (0.0,0.7) cm and the LOS pressure increased by 7.6 (5.4,14.5) mmHg after completion of the MWS. (Table 5.9)

8 out of 10 subjects had a post-MWS effective 'clearing' peristalsis event and 8 out of 10 also had an effective LOS after-contraction. (Figure 5.14)

	Healthy (n=10)			
	Median (IQR)	5th %ile	95th %ile	Mean ±SE (SD)
MWS number of swallows	15.5 (11.8, 20.3)	10.5	23.8	16.3±1.1 (5.3)
MWS duration (s)	22 (19,29)	15	33	23±1 (7)
MWS suppression of contractility (0 - no contractions, 1 almost complete, 2 partial, 3 minimal, 4 no suppression)	0 (0.0,0.0)	0	0	0.0±0.0 (0.0)

Table 5.8 Oesophageal function during and after multiple water swallows (MWS) for 10 healthy volunteers.

	Healthy (n=10) Median (IQR)
Swallows until LOS relaxes (≤15mmHg)	2 (0,3)
Swallows until LOS relaxes (corrected to No of swallow %)	13% (0%,21%)
Time from start of MWS → LOS relaxation (s)	1.8 (0.0,2.8)
Time until LOS relaxes (≤15mmHg) (corrected to total time to complete the drink %)	8% (0%,14%)
LOS distance from preto post MRS (cm)	0.3 (0.0,0.7)
MWS P difference pre and post MRS (mmHg)	7.6 (5.4,14.5)
Estimated volume per swallow (ml)	13.5 (9.9,17.2)
Estimated volume until LOS relaxes (ml)	25.6 (0.0,42.1)

Table 5.9 Secondary analysis results for Multiple Water Swallows (MWS) in 10 healthy volunteers.

(LOS = Lower oesophageal sphincter; P = pressure)

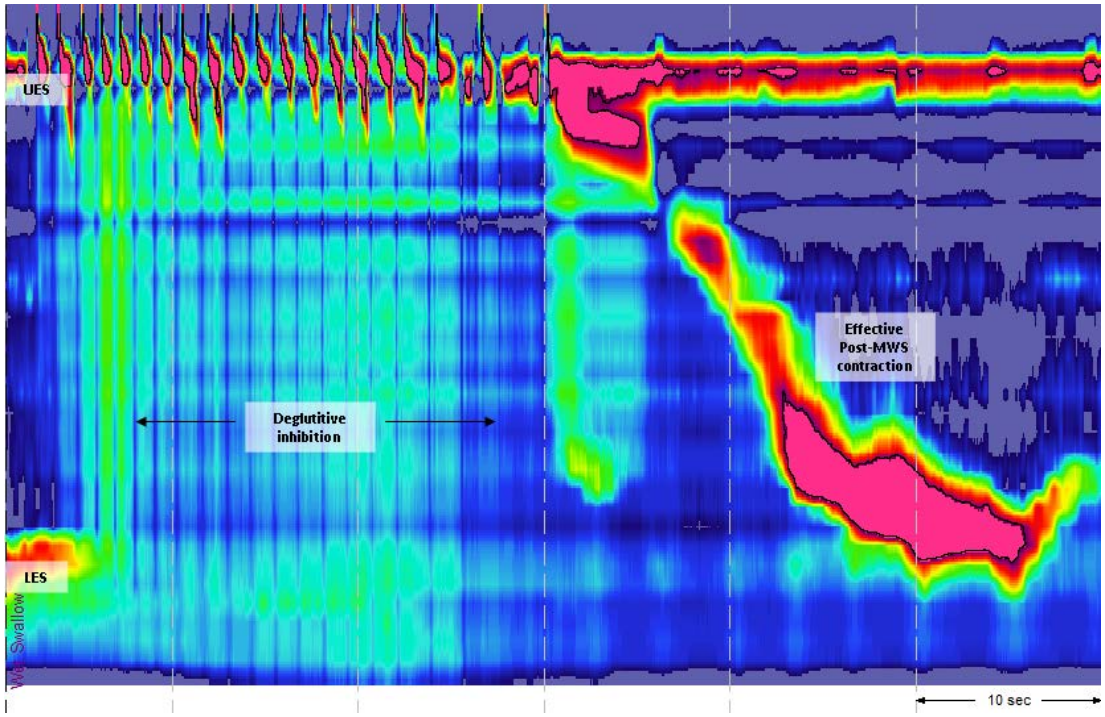


Figure 5.14 High resolution manometry of a normal 200 ml water swallow showing deglutitive inhibition and relaxation of the oesophagus and LOS followed by an effective 'clearing' post-MWS peristalsis and LOS after-contraction. In this example 5/19 pharyngeal swallows were required to open the LOS at 15 mmHg (isobaric contour) after which water passed freely into the stomach. The post-peristalsis LOS contraction also prevented reflux of gastric content.

5.3.3 Symptoms

No healthy volunteer complained of symptoms during the water, bread or test meal study. Therefore a symptom-dysmotility association analysis was not performed; however this will be described in detail in Chapter 6.

Post-prandial observation

During the 10 minute post-meal observation period, healthy participants exhibited a median (IQR) of 2.0 (1.3,3.5) episodes of spontaneous (TLOSR) and 1.0 (0.0,1.0) swallow-related (SLOSR) relaxations of the LOS with common cavity events. These were associated with a median (IQR) of 2 (2,4) belch events. Furthermore, a gradual LOS drift >10 seconds with loss of pressure but no common cavity was seen in 3/10 healthy volunteers over a median of 15 (maximum 25) seconds. No volunteer complained of adverse symptoms (discomfort, chest pain, nausea or vomiting). (Table 5.10) A representative post-prandial HRM plot typical of a healthy individual is shown in Figure 5.15.

	Healthy (n=10)
TLOSR	2.0 (2.0,3.5)
TLOSR + CC	2.0 (1.3,3.5)
SLOSR	1.0 (0.0,1.8)
SLOSR + CC	1.0 (0.0,1.0)
Total LOSR	3.5 (2.3,4.8)
Total LOSR + CC	3.0 (2.0,4.0)

Table 5.10 Post meal observation in 10 healthy volunteers. Parameters are presented as median (IQR)

(TLOSR = Transient lower oesophageal sphincter relaxation; SLOSR = Swallow-related lower oesophageal sphincter relaxation; CC = common cavity)

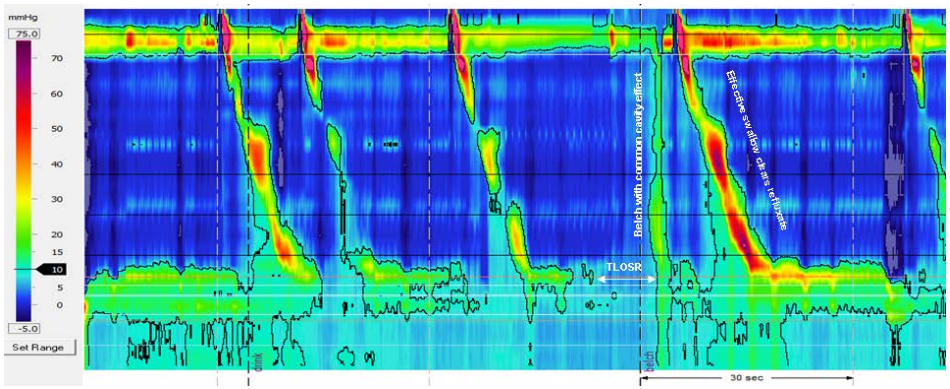


Figure 5.15

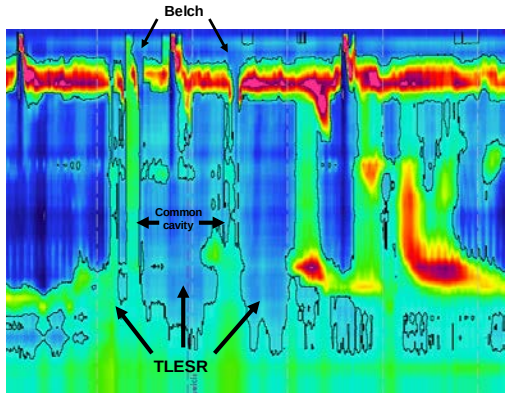


Figure 5.15b

Figure 5.15 Post meal observation period in a healthy volunteer (a) A typical HRM trace showing 1 SLOSR followed by a common cavity event and belch. This was then followed by an effective 'clearing' peristalsis. (b) Example of a common cavity event with 3 TLOSRs as well as 2 associated belch events.

5.4 Summary of results

- High Resolution Manometry can be used to measure physiological, clinically relevant swallows of liquids and solids in the upright seated position.
- As workload on oesophageal function increased with movement from the upright to the supine position and from liquid to solid swallows, oesophageal contractile response was slower (lower contraction front velocity), better coordinated (shorter proximal transition zone) and more vigorous (greater distal contractile integral).
- There was significant agreement between independent observers for manually measured parameters during liquid and solid swallows derived from HRM spatiotemporal plots in both positions and viscosities; intra-class correlation coefficient between 3 assessors was >0.5 for all parameters measured
- Results presented in this chapter can be used as reference values and the technique can be replicated in clinical practice. These were used to study the effects on patients in Chapter 6.

5.5 Discussion

The most appropriate and clinically relevant measurement protocol for oesophageal manometric studies has not been established. Currently, for both conventional and high resolution manometry, diagnostic classifications are based on repeated small volume swallows of water in the supine position.[113,131] This non-physiological testing method does not represent normal behaviour and symptoms are rarely triggered. It has been suggested that using the physiological, upright seated position and including solid swallows increases the sensitivity to symptomatic dysmotility and dysfunction;[270,271,273,274,280,281] however this is not routine practice, a standardised method is not available, reference values have not been established and interpretation of data is more complex. High resolution manometry, with its spatiotemporal representation of pressure data, can facilitate the analysis of oesophageal motility,[282] and can provide a better understanding of oesophageal function and structure during 'challenge swallows' (e.g. solids). Studies presented in this chapter propose a conceptual shift in the assessment and classification of oesophageal motility. Instead of restricting to small volume water swallows in the supine position, normative values for key HRM parameters of peristaltic and OGJ function are presented for swallows of different volumes, consistencies and positions. Furthermore inter-observer agreement provides confidence that these techniques are reliable and reproducible.

Standard parameters of oesophageal function for liquid swallows in the supine position (LOS basal and relaxation pressure, peristalsis velocity) were similar to published values.[131] Only contractile pressures and DCI were somewhat lower than those reported by Ghosh et al.[125] which used HRM equipment from the same manufacturer (Manoview). Although the reason for this is not clear, it is likely related to differences in demographic factors between the population groups in each study (e.g. age, obesity and racial background).[50,283,284] The effects of position and bolus consistency on oesophageal function were consistent with previous studies using standard and high resolution manometry.[36,137,244]

The most important findings in this chapter were that in healthy subjects as the workload on the oesophagus increased with movement from the upright to the supine position and in particular from swallowing liquids to solids, oesophageal contractile

response was slower (slower contraction front velocity (CFV)), better coordinated (shorter proximal transition zone (PTZ) with increased nadir pressure) and more vigorous (greater distal contractile integral (DCI)). (Tables 5.2-5.4) Bolus characteristics and position change both affect the coordination of peristaltic contraction in healthy, asymptomatic volunteers by promoting contractility in the distal segment. Preservation of the oesophageal response to solid bolus or swallowing in the supine position may provide useful options to test the oesophagus' ability to respond to 'physiological challenge' (which increases workload on the oesophagus).

Although normal LOS relaxation was observed for all swallows, IRP increased during solid swallows compared to liquids. Possible explanations for this phenomenon are that there may be more friction between the solid bolus and the luminal wall.[126] In addition, there was a small but consistent rise in IRP from the supine to the upright seated position. This was unexpected and is likely to be due to the increased hydrostatic forces in the distal oesophagus in the upright position. Also changes in OGJ anatomy may alter resistance to flow across the OGJ during this shift in position.[285] Further testing with fluoroscopy or MRI studies may help describe this phenomenon.

The coefficient of variation (CV) was used to identify the degree of intra-individual variation for each parameter, and indeed there was a high degree of variation for all measurements. This was particularly true for point measurements of contractility and distal segment contractile vigour (DCI) for which CV exceeded 100%. These findings confirm previous reports of increased variation in healthy individuals[125,131,247] (as well as in patients; Chapter 6). More importantly, the high frequency of 'abnormal' yet asymptomatic peristalsis (especially hypotensive, hypertensive and simultaneous contractions) in healthy individuals demonstrates that manometric findings should not be classified as 'dysfunction' or considered abnormal unless they are coupled with symptoms; a concept that will be further explored in Chapter 6.

Even among experts in specialist centres, the inter-observer agreement for manometric classification of individual water swallows using conventional manometry is only fair to moderate.[269] Until now, an inter-observer assessment for HRM findings during solid swallows or position shift has not been performed in

routine practice. Semi-automated analysis of key parameters is provided by the proprietary software; however all require accurate pre-analysis demarcation of swallow margins and re-positioning of markers (described in Chapter 2). This becomes considerably more arduous with 'challenge' swallows (single solid and test meal). Nevertheless, this chapter demonstrates that despite the increased level of complexity, such novel techniques and measurements are easy to learn and are reproducible as significant agreement was achieved between independent observers for manually derived parameters during challenge swallows even after only a brief initial period of training. It is interesting to note that inter-observer agreement for peristaltic velocity and, to a lesser extent other parameters, was reduced in the upright than the supine positions. The observers reported that this was often a result of difficulty in the placement of measurement landmarks in the upright position due to reduced coordination (wide proximal transition zone) and low contractile pressures, especially with water swallows. This was not unexpected, and was clearly seen in Table 5.2-5.4 and Figure 5.5; contractility decreased and PTZ widened significantly from the supine to the upright seated position as workload reduced and the oesophagus relies more on gravity for bolus transport. Nevertheless, when looking at results from all healthy subjects, there was no statistical difference in the vigour of contractility (DCI) nor in the bolus transport velocity (CFV) between the upright and supine positions for either consistency (Table 5.2 and 5.4 and Figures 5.8-5.10). Furthermore, when corrected for total oesophageal length, PTZ coordination (% distal segment length) did not change for solids when moving from the upright to the supine position. (Table 5.3) These findings imply that, at least for solid swallows, the upright position imposes sufficient force which is at least comparable to the supine. On the other hand, as the upright position was better tolerated and more physiological and as solid swallows increase the workload on the distal oesophagus, it was considered the preferred method for patient testing at St Thomas' Hospital. Chapter 6 will show that compared to water alone, swallowing solids in the upright position and consuming a standardised meal was a better discriminator for identifying pathology than with water swallows as relevant symptoms were more likely to be induced.

It is important to describe why ICC (intra-class correlation coefficient) was preferred to Kappa analysis for inter-individual variability. Kappa analysis is most suitable for comparing 2 assessors and although the Fleiss statistic can be used to extend the

measure to multiple assessors both Kappa and Fleiss statistic of analysing inter-assessor agreement are suitable only for nominal or ordinal-level data,[286] while quantitative measurements were compared in this study.

Compared to the standard small volume water and bread swallows, DCI, coordination and (in most cases) intra-bolus pressure improved with the increased workload of the standardised meal (Table 5.7, Figure 5.11b). These findings are consistent with results from previous studies.[36,126] Interestingly IRP appeared not to change (Table 5.7, Figure 5.11a). One possible explanation is because unlike the continuous nadir pressure used in early manometric measurements, the automated IRP parameter chooses 4 continuous or non-continuous seconds with the lowest mean pressure across the LOS within the deglutitive period while gastric pressure remains a stable reference.[134] Therefore, as long as there is no intrinsic and continuous structural resistance to flow or functional pathology at the OGJ (i.e. as long as there is a non-continuous 4 second period within the deglutition in which IRP relaxes) effective clearance can be achieved and IRP should be normal.

Stationary HRM studies can provide insight into the structure and function of the OGJ (LOS pressure, intra-abdominal LOS length, hiatus hernia size) in more detail than conventional manometry.[247,287] However in the absence of concomitant impedance-pH monitoring or fluoroscopy, baseline HRM measurements using 5ml water swallows are not able to predict the severity of reflux or the likelihood that symptoms may occur during or after meals. On the other hand after the standardised meal a 10 minute postprandial observation period provided insight into the behaviour of the OGJ in the healthy oesophagus. After a refluxogenic test meal and smoothie, transient (TLOSR) and swallow associated (SLOSR) lower oesophageal spincter relaxations were observed in healthy subjects. Many of these were accompanied by common cavity events (i.e. reflux); however almost all of these were then followed by a well coordinated ‘clearing’ peristalsis. Moreover, apart from the occasional belch, subjects were almost never conscious of these events taking place. This study standardised the methodology and analysis technique for the postprandial observation period (see Chapter 6 for the assessment of patients).

5.6 Conclusion

This study provided normative values for oesophageal peristalsis and oesophago-gastric junction function in healthy individuals during the physiological upright seated position. Single water and bread swallows were followed by free drinking and, in those who consented, a reflux provoking test meal which was typical of a western diet. Then a brief post-prandial observation period assessed the mechanistic effect of the OGJ and oesophagus. HRM spatio-temporal plots for upright single swallows were compared with standard supine swallows for both liquid and solid swallows. Significant differences for key variables measured in the upright and supine positions and for liquid, solid and test meal swallows confirmed that the oesophagus responds predictably to increased workload by improving coordination, increasing contractility and reducing velocity of peristalsis. Variations in response to body position and bolus consistency imply that different normative values should apply for every study condition. Taken together, the consistency of these results with the literature (e.g. supine water swallows) and the positive inter-observer agreement provide assurance that measurements acquired using these techniques are valid and can be reliably applied in research and in clinical practice. Normative values methodology presented here were used in the assessment of patients in Chapter 6.

Chapter 6

Diagnostic yield of High Resolution Manometry in patients presenting with oesophageal symptoms

6.0 Introduction

Dysphagia and other symptoms associated with impaired oesophageal function usually occur while consuming food or drink. Heartburn and symptoms of gastro-oesophageal reflux occur mostly after meals. Presenting symptoms alone are an unreliable guide to identifying oesophageal dysfunction.[15,16] If clinical history and endoscopy are inconclusive then guidelines recommend oesophageal manometry and pH studies;[78,288] however in many patients conventional manometry (with 5-8 pressure sensors) also fails to establish the cause of symptoms.[111,126] Furthermore, the clinical relevance of this assessment is open to question because small volume water swallows are not representative of normal drinking and eating behaviour as they do not 'challenge' oesophageal function and rarely trigger symptoms.

Presently normal values for both conventional and high resolution manometry (HRM) are obtained from 5 ml water swallows in the supine position.[78,125,247,288] In Chapter 5 HRM normative values were presented and a high inter-observer agreement was documented for both water and bread swallows in the standard supine and physiological upright seated positions.[275] Consistent with previous studies in healthy volunteers,[36,137,244] the oesophagus responded to the 'physiological challenge' of changing position and bolus consistency by improving coordination and increasing the vigour of peristaltic contractions. In patients, Daum et al[245] showed that similar results were seen with non-erosive reflux disease; however failure to respond to the 'challenge' of solid swallows was associated with pathological acid exposure on ambulatory pH-studies and the presence of erosive oesophagitis. This suggests that HRM studies with bread swallows increase sensitivity to clinically relevant dysfunction. This chapter tested the hypothesis that the same methodology should also demonstrate a mechanistic link between oesophageal dysfunction and oesophageal symptoms.

The diagnosis of gastro-oesophageal reflux disease (GORD) is established with ambulatory pH studies either on the basis of increased oesophageal acid exposure or the association of reflux events with symptoms.[2] The latter provides a direct explanation for patient symptoms[289] and can guide management.[77,151,175,268] As yet ambulatory HRM is not available but stationary HRM facilitates the description of complex pressure events that are induced with solid swallows and identifies

symptomatic dysfunction not detected by conventional studies;[111,290] however a standardised dysmotility-symptom association parameter has not yet been proposed. Additionally, as demonstrated in the previous chapter, HRM facilitates the assessment of the oesophago-gastric junction (OGJ) and the degree of separation between the intrinsic and diaphragmatic components of the OGJ in hiatus hernia. It can also identify transient lower oesophageal sphincter relaxation (TLOSR), reflux (common cavity) and other events (such as rumination) that typically occur after meals.[52,130,285,291,292]

6.1 Aims

The detection of abnormal pressure events in close temporal association with symptoms has inherent face validity. A novel methodology for HRM analysis of oesophageal function during a standardised test meal, free drinking and the post-prandial period was presented in Chapter 5. The aim of this chapter was to provide an assessment of oesophageal motility and function in patients with endoscopy negative dysphagia, chest pain and symptoms suggestive of gastro-oesophageal reflux.[78,113] Results from healthy volunteers presented in Chapter 5 were compared with patients. A novel parameter that measures the association between dysmotility and symptoms (similar to the Symptom Index of ambulatory pH studies) was proposed. The final diagnosis, management and outcome of patients were assessed at 2 years follow-up to provide insight into the reliability and clinical utility of this methodology.

Hypothesis: In patients with symptoms of reflux and dysphagia, eating and drinking will identify pathology and induce symptoms not seen with standard small volume water swallows. Furthermore these finding based on these techniques should influence management decisions.

6.2 Methods

(please refer to Methods Chapter 2; additional methodology specific for this study will be described here)

6.2.1 Study design

This was a prospective study of patients presenting with typical symptoms of reflux with/without dysphagia. Patients underwent a similar protocol to healthy volunteers described in the Methods of Chapter 2 and Chapter 5, albeit only in the physiological upright position; small volume single bolus water and bread swallows, free drinking, standardised test meal and post-prandial observation. Measurements associating symptoms with dysmotility were determined. Patients were then followed up to two years after initial diagnosis.

6.2.2 Patients

18 patients were referred for investigation of typical GORD-like symptoms (heartburn, acid regurgitation) of whom 7 also had symptoms of dysphagia. All patients completed five x 5 ml water and five x 1 cc bread swallows. This was followed by free drinking of 200 ml of water through a straw (Multiple Water Swallow; MWS) and eating of a refluxogenic test meal (cheese and onion pie and 200ml fruit smoothie). The study was terminated after a 10 minute postprandial observation period. Reference values from the 10 healthy volunteers who completed the study protocol (Chapter 5) were used to define pathology. (For inclusion/exclusion criteria please refer to Appendix 8)

6.2.3 Data Analysis

Data acquisition and analysis was identical to that described in Methods sections of Chapter 2 and Chapter 5. Primary analysis compared the occurrence of oesophageal dysmotility, symptoms and their association in both healthy volunteers and patients. A secondary analysis compared patients with pathological (GORD) and normal (Functional Heartburn; FH) results on ambulatory pH monitoring.

Single bolus swallows

Single swallows of 5 ml water and 1 cc bread were performed in the physiological upright position. Details of the metrics analysed was presented in section 5.2.3.

Standardised test meal

I. Primary HRM parameters for meal studies were similar to single bolus swallows:

- Integrated Relaxation Pressure (IRP)
- Contractile Front Velocity (CFV)
- Breaks in the 30 mmHg pressure contour
- Distal Contractile Integral (DCI)
- Intra-bolus Pressure (IBP)

II. Primary HRM functional measurements included:

- the frequency of successful/ineffective/failed peristalsis following every pharyngeal swallow

III. Primary MWS functional measurements included:

- Total volume
- Total number of swallows
- Total time required to complete the drink
- A semi-quantitative assessment of oesophageal motor suppression
  0 = complete inhibition of contractility
  1 = almost complete (<3cm contraction) inhibition
  2 = partial (incomplete peristaltic contractions or spasm) inhibition
  3 = minimal (complete peristaltic contraction or spasm) inhibition
  4 = repeated contractions / no inhibition
- Presence/absence of a post-MWS clearance contraction
- Presence/absence of a post-MWS LOS after-contraction.

IV. Primary post-meal functional measurements included:

- Frequency of Transient LOS relaxations (TLOSRs)
- Frequency of Swallow-related LOS relaxations (SLOSRs)
- Frequency of common cavity (reflux) events in both TLOSRs and SLOSRs
- Total number of other events that may be associated with reflux (e.g. slow drift of LOS pressure to zero, rumination)

Association of pressure events with symptoms

Only symptoms volunteered by the patient were recorded on the HRM spatio-temporal plot and were included in the analysis. Symptom-associated oesophageal dysfunction (SAD) was defined as a symptom event reported up to 10 seconds after a dysmotility or dysfunction (including reflux) event on HRM. Oesophageal Dysfunction-Symptom Index (D-SI) was defined as the number of SAD events divided by the total number of symptoms reported during each study.

$$\frac{\text{Symptom Associated Dysfunction (SAD)}}{\text{Total No. Symptoms}} \times 100 = \text{Oesophageal Dysfunction Symptom Index (D-SI)}$$

This parameter was similar to Reflux-related Symptom Index described during ambulatory reflux studies. (Methods Chapter 2, Chapter 3 and 4) D-SI was assessed with a diagnostic cut-off >50%

Dysmotility episodes were not used as the denominator (i.e. a parameter akin to the Symptom Sensitivity Index) as it would not be possible to differentiate between 'dysmotility' leading to dysfunction and normal function; up to 49% of swallows in asymptomatic healthy individuals were not peristaltic and many of these were non-propagating pharyngeal swallows. (Chapter 5)

24 hour catheter-based pH monitoring

All patients had 24 hour catheter-based pH monitoring (C-pH) using Digitrapper™ Slimline™ (Medtronic Inc., Shoreview, MN) while off acid suppressant medication.[259] A standard technique for preparation, investigation and analysis was employed (see Methods Chapter 2). Total Reflux (TR; percentage oesophageal acid exposure below pH 4) was the primary outcome measurement on which GORD diagnosis was based and standard diagnostic cut-offs were implemented.[78,85,103,250] A symptom event was considered to be related to a preceding reflux event if it occurred within 2 minutes. Reflux Symptom Index (SI) was assessed with a diagnostic cut-off >50%.[255]

Diagnosis and follow-up

HRM findings and diagnosis based on the physiological challenge techniques and novel metrics described above were compared with the clinical outcome up to 2 years follow-up. Follow-up was based on patient self-reported outcome assessment and/or referring physician/surgeon written/verbal assessment of progress. (See Chapter 2)

6.2.4 Statistical analysis

Mann-Witney and Wilcoxon tests were used for nonparametric comparisons of quantitative swallow parameters between and within groups respectively. $P<0.05$ was considered statistically significant. Friedman test was used for analysis of variance for multiple comparisons of nonparametric data within groups (i.e. comparing water, bread and test meal parameters within the same patient group). Fisher exact test was used to assess the difference in the frequency of effective and ineffective oesophageal and LOS aftercontraction between the groups.

Pearson's coefficient (PC) assessed the strength of relationship between the frequency of effective swallows and the total time required to consume meals between healthy subjects and those presenting with symptoms.

6.3 Results

6.3.1 Participant demographics

10 asymptomatic healthy volunteers (male:female 6:4, age 20-45; described in Chapter 5) and 18 patients (male:female 5:13, age 32-76) were recruited. Patients reported heartburn (n=17) and/or acid regurgitation (n=12) as well as dysphagia (n=7), chest pain (n=8) and one had recurrent cough. (Figure 6.1)

Endoscopy

Endoscopy findings included 8 with normal mucosa (i.e. non-erosive mucosa and no hiatus hernia), 4 with grade A oesophagitis and 3 with a short (<3 cm) segment of Barrett's oesophagus. Endoscopically, a small hiatus hernia (<3 cm) was visualized in 7 patients overall. (Figure 6.2)

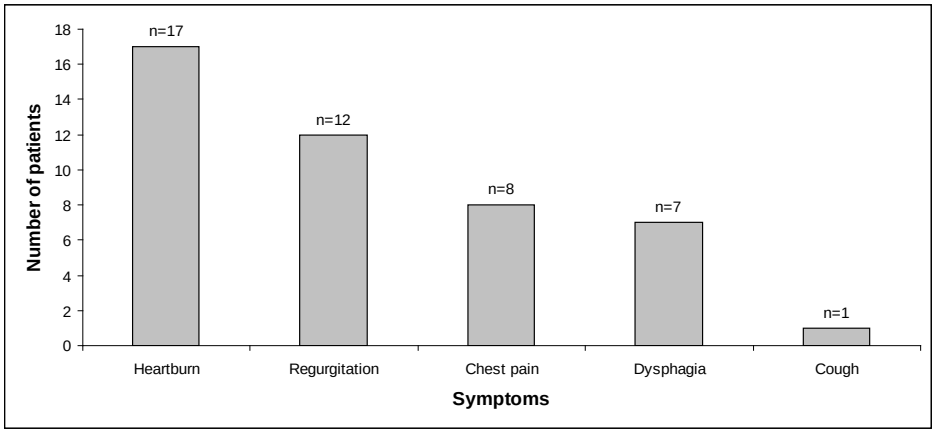


Figure 6.1 Overall distribution of patient symptoms at presentation to the St Thomas' Hospital Oesophageal Lab.

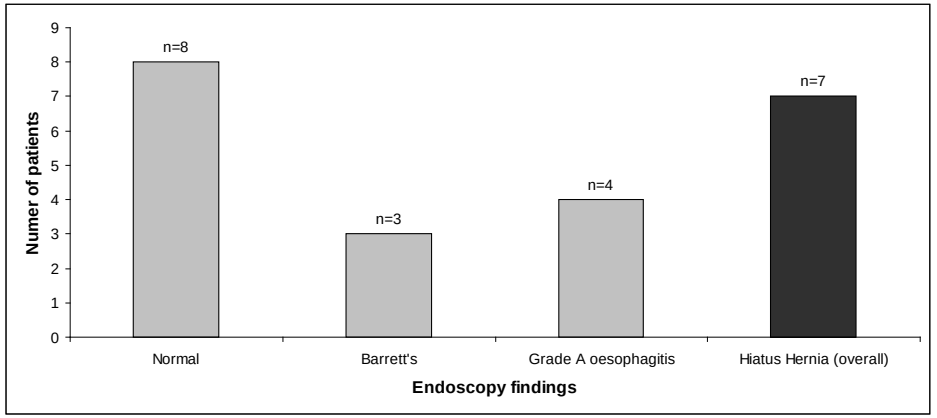


Figure 6.2 Endoscopy findings among the 18 patients studied. 7 patients had hiatus hernia overall, 4 of whom also had Barrett's oesophagus or Grade A oesophagitis.

Manometry and ambulatory pH monitoring

Manometry was tolerated and technically adequate swallows were acquired for water swallows and the test meal for all volunteers and patients. One patient stopped the post-meal observation early due to intolerance. Following ambulatory pH monitoring, 11/18 (65%) patients had a diagnosis of GORD based on a pathological total oesophageal acid exposure (TR; median 11.1% (IQR 6.4%,15.5%)). Of those, 9 also had a positive reflux-symptom association (SI >50%); 5 for heartburn alone, 3 for regurgitation alone and 1 for heartburn, regurgitation and chest pain together. The remaining 7 patients (39%) had normal acid exposure (median 0.9% (IQR 0.1%,1.8%)) and no reflux-symptom association with ambulatory reflux studies (i.e. Functional Heartburn (FH)). 3 of these had no dysphagia symptoms at presentation.

6.3.2 Water, bread and meal swallows in healthy subjects and patients: Motility and Function

As was seen with healthy subjects (Chapter 5), during the test meal patients exhibited an improvement in co-ordination (shorter PTZ length; Friedman $p<0.001$ and increased PTZ nadir pressure; Friedman $p<0.001$) as well as a more vigorous distal contractile force (DCI; Friedman $p=0.003$) compared to 5ml water and bread swallows. There was no change in IRP between bread and test meal ($p=0.396$). Compared to water swallows, although IRP was greater during the test meal, this did not quite achieve statistical significance ($p=0.061$). There was no change in contractile velocity of the distal segment between water, bread and meals ($p=0.936$). (Table 6.1)

In the GORD group (n=11), IRP, IBP, DCI and PTZ nadir pressure increased and PTZ length decreased with the standardised meal compared to water or bread (Friedman $p<0.05$ for all). This suggests a more peristaltic, coordinated and vigorous contraction. Although changes in velocity were not significant, semi-automated landmarks were not always easily applicable during the test meals thus making accurate calculation difficult. (Table 6.2 and Figure 6.3).

7/18 (39%) patients had normal measurements on pH monitoring and were defined as having Functional Heartburn (FH). Of these 4/7 (57%) had symptoms of dysphagia at presentation. All 7 patients also had symptoms of heartburn ± regurgitation or chest pain. (Table 6.3) In this group, IRP and IBP did not change from water swallows to the standardised meal, nor was there a difference in the distal contractile vigour or front velocity (p=NS for all). On the other hand, coordination did significantly improve from water to standardised meal; shortened PTZ length and raised PTZ nadir pressure (p=0.027 and 0.028 respectively). (Table 6.3 and Figure 6.4)

	5ml WATER SWALLOW		1cc BREAD SWALLOW		STANDARDISED MEAL		p	p	p
	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	(water vs meal)	(bread vs meal)	(Friedmanl)
IRP (mmHg)	5.4 (4.6,8.3)	7.8±1.4 (5.8)	9.3 (6.9,12.5)	10.4±1.2 (5.0)	7.2 (5.4,16.5)	10.6±1.7 (7.3)	0.061	0.396	0.006
IBP (mmHg)	12.4 (6.9,15.6)	12±1.4 (5.9)	15.4 (11.0,21.9)	16.3±1.6 (6.7)	19.2 (14.5,26.5)	23.3±3.0 (12.6)	0.001	0.010	<0.001
PTZ break P (mmHg)	12.2 (9.9,15.8)	12.9±1.2 (4.9)	18.2 (15.0,29.2)	22.5±2.5 (10.4)	26.4 (23.7,39.7)	31.1±3.0 (12.7)	0.003	0.004	<0.001
PTZ length (cm)	4.5 (2.8,6.8)	4.8±0.6 (2.6)	2.4 (1.5,3.7)	2.4±0.4 (1.5)	1.0 (0.2,1.6)	1.3±0.4 (1.5)	0.001	0.011	<0.001
CFV (cm/s)	3.8 (2.9,4.4)	3.6±0.3 (1.1)	3.3 (2.9,4.5)	4.9±0.5 (2.0)	2.9 (2.5,7.3)	8.4±2.6 (11.1)	0.605	0.955	0.936
DCI (mmHg $cm^{-1}s^{-1}$)	678.0 (358.5,1250.0)	973.3±206.6 (876.6)	768.3 (572.0,1402.8)	1112.7±211.0 (895.1)	1009.3 (686.7,3156.8)	1736.9±336.6 (1427.9)	0.003	0.006	0.003

Table 6.1 Key parameters describing oesophageal motility and function for all (n=18)

	5ml WATER SWALLOW		1cc BREAD SWALLOW		STANDARDISED MEAL		p	p	p
	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	(water vs meal)	(bread vs meal)	Friedman
IRP (mmHg)	5.2 (3.1,5.8)	5.4±1.2 (3.7)	7.2 (6.3,11.1)	8.4±1.1 (3.5)	6.3 (4.8,8.6)	8.7±2.0 (6.3)	0.021	0.477	0.029
IBP (mmHg)	12.2 (6.8,16.2)	11.9±2.1 (6.7)	14.4 (11.1,19.3)	15.7±2.3 (7.6)	20.2 (15.1,29.7)	25.6±4.7 (14.8)	0.007	0.007	0.002
PTZ break P (mmHg)	12.8 (10.0,17.2)	14.4±1.5 (4.8)	17.2 (14.4,28.5)	21.4±3.5 (11.5)	38.2 (20.3,41.0)	32.2±4.5 (14.2)	0.021	0.050	0.012
PTZ length (cm)	2.9 (2.5,5.4)	4.1±0.9 (2.8)	2.4 (1.4,3.1)	2.1±0.4 (1.4)	0.6 (0.2,1.8)	1.5±0.6 (1.9)	0.008	0.241	0.001
CFV (cm/s)	4.2 (3.0,4.4)	3.7±0.4 (1.3)	3.3 (2.8,3.9)	3.8±0.6 (2.1)	4.2 (2.2,8.8)	8.0±2.7 (8.6)	0.066	0.477	0.913
DCI (mmHg $cm^{-1}s^{-1}$)	517.6 (232.0,707.0)	770.0±294 (928.4)	591.6 (408.1,781.2)	906.9±269.8 (894.9)	855.9 (522.3,1291.8)	1352.5±434.5 (1374.1)	0.038	0.091	0.078

Table 6.2 Key parameters describing oesophageal motility and function in patients with objective evidence of GORD following ambulatory pH studies. (n=11)

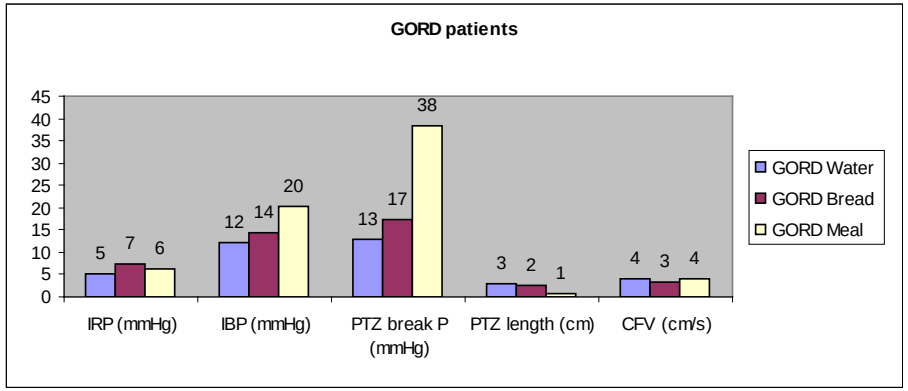


Figure 6.3a

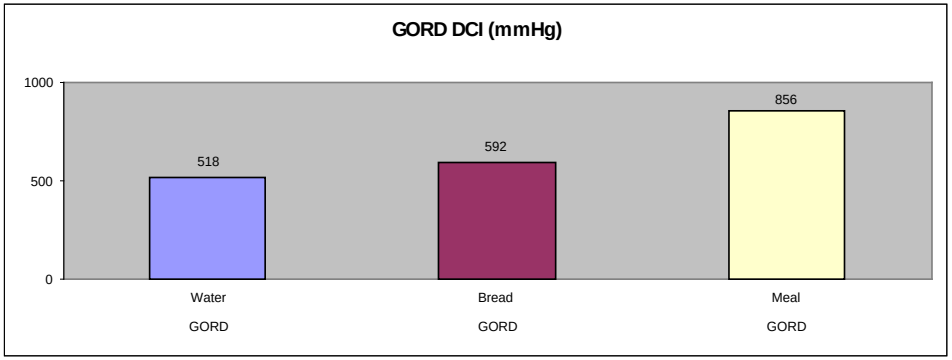


Figure 6.3b

Figure 6.3 Effect of changing bolus consistency (water, bread, meal) for primary parameters known to affect bolus transport in patients with GORD (n=11). Results are presented as median values.

(IRP = Integrated Relaxation Pressure; IBP = Intra-bolus Pressure; PTZ = Proximal Transition Zone; CFV = Contractile Front Velocity; DCI = Distal Contractile Integral)

Note: p-values for Wilcoxon (between water, bread and test meal) and Friedman (overall change between modalities) are presented in Table 6.2.

	5ml WATER SWALLOW		1cc BREAD SWALLOW		STANDARDISED MEAL		p	p	p
	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	Median (IQR)	Mean±SE (SD)	(water vs meal)	(bread vs meal)	Friedman
IRP (mmHg)	8.4 (6.7,16.2)	11.5±2.5 (6.6)	10.8 (9.3,18.6)	13.5±2.1 (5.7)	10.7 (7.2,19.1)	13.5±3.1 (8.3)	0.799	0.735	0.156
IBP (mmHg)	12.6 (9.6,14.7)	12.3±1.8 (4.7)	17.8 (13.3,21.7)	17.2±2.0 (5.3)	19.2 (14.3,24.9)	20.0±3.1 (8.3)	0.063	0.611	0.021
PTZ break P (mmHg)	9.8 (6.4,12.4)	10.1±1.5 (4.1)	21.4 (17.0,28.7)	24.2±3.4 (9.0)	25.9 (24.4,26.6)	29.3±4.0 (10.5)	0.028	0.116	0.009
PTZ length (cm)	7.3 (5.3,7.4)	6.1±0.8 (2.0)	3.1 (1.8,4.1)	2.8±0.6 (1.6)	1.3 (0.5,1.5)	1.1±0.3 (0.8)	0.027	0.028	0.002
CFV (cm/s)	3.6 (2.9,4.0)	3.6±0.3 (0.8)	3.7 (3.1,4.9)	4.4±0.7 (1.9)	2.8 (2.6,3.4)	9.1±5.8 (15.4)	0.600	0.138	0.247
DCI (mmHg $cm^{-1}s^{-1}$)	1284.0 (1148.0,1586.5)	1339.3±270.8 (716.4)	1156.5 (844.5,2095.5)	1455.7±324.2 (857.9)	2319.0 (1151.3,3595.5)	2377.7±525.0 (1389.1)	0.173	0.028	0.042

Table 6.3 Key parameters describing oesophageal motility and function in patients with Functional Heartburn (n=7).

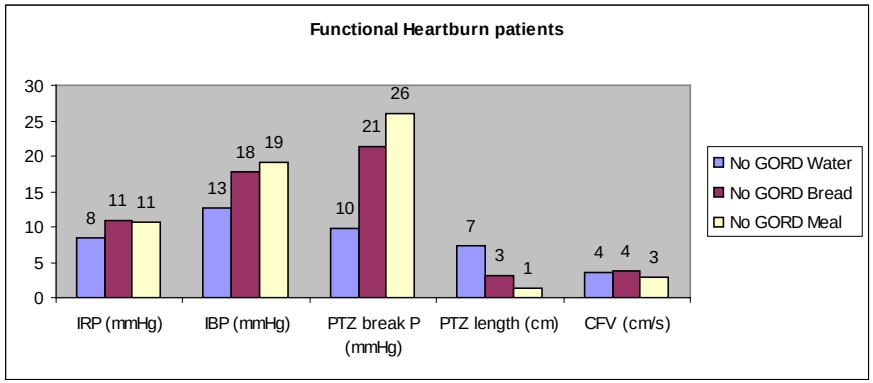


Figure 6.4a

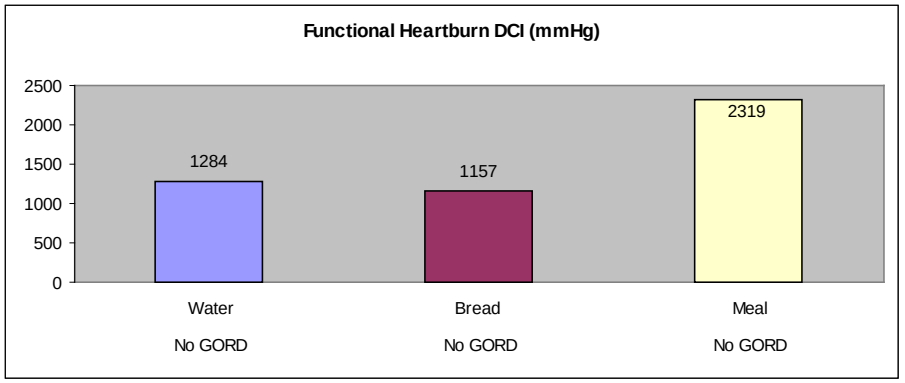


Figure 6.4b

Figure 6.4 Effect of changing bolus consistency (water, bread, meal) for primary parameters known to affect bolus transport in patients with Functional Heartburn (n=7). Results are presented as median values. p-values for Wilcoxon and Friedman tests are presented in Table 6.3

Lower oesophageal sphincter (LOS)

Comparing the study groups, there was no significant difference in LOS baseline pressure between healthy subjects (19.0 (11.8, 27.7) mmHg) and patients (18.4 (9.8, 25.4) mmHg; p=0.649). Nor was there a difference compared to those with Functional heartburn (18.8 (18.4,31.1) mmHg; p=0.536). Although patients with GORD had a lower median LOS (10.4 (9.6, 20.8) mmHg) this did not achieve statistical significance (p=0.245).

The total LOS length was similar in healthy subjects and all patients (3.2 (2.9,3.2) cm vs. 3.1 (2.8,3.6) cm; p=0.981) and this did not change during a sub-analysis of those with GORD (3.0 (2.4,3.3) cm; p=0.458) and Functional heartburn (3.2 (3.1,3.7) cm; p=0.325); however intra-abdominal LOS length was greater in healthy subjects than patients as a whole (2.3 (1.6,2.7) cm vs. 1.3 (-1.0,2.1) cm; p=0.023) and those with GORD (0.5 (-2.6,2.0) cm; p=0.014) but not in those with Functional heartburn (1.6 (1.0,1.9) cm; p=0.221). Hiatus hernia was demonstrated HRM in 5 (28%) patients all of whom had GORD on ambulatory pH studies with an overall range of 1.4 - 6.4 cm. Three of those had hiatus hernia identified at endoscopy and 2 did not. On the other hand, three other patients who were described as having a small hiatus hernia at endoscopy showed no separation of the LOS components during manometry at rest nor during challenge swallows.

6.3.3 Swallow effectiveness during the test meal

During the standardised test meal, the median consumption time of 552 (range 492,720) seconds was similar in healthy subjects and patients (p=0.132). A median 33 (IQR 29,42) pharyngeal swallows were required to complete the meal in patients. This was similar to healthy subjects (Chapter 5) in whom the median consumption time for the standardised meal was 399 (range 307-550) and the median number of pharyngeal swallows required to complete the meal was 29 (IQR 27,32). An HRM trace representative of a test meal in a patient with typical symptoms of reflux is shown in Figure 6.5.

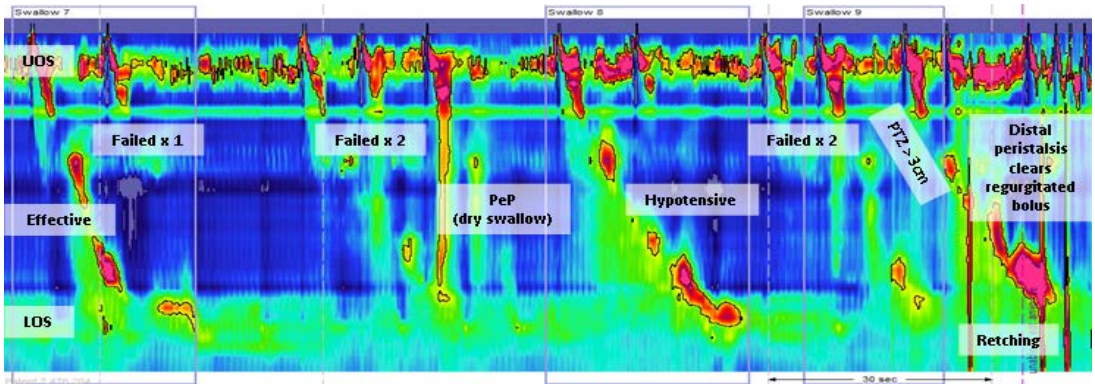


Figure 6.5 HRM trace of a patient with GORD following a refluxogenic test meal. 30 mmHg isobaric contour was applied. A oesophageal function after every phyarngeal swallow is labelled.
(PeP = Pan-oesophageal pressurisation. PTZ = Proximal transition zone.)

Compared to healthy subjects, fewer effective swallows were observed in patients overall (51% vs. 28%; $p<0.001$) (Figure 6.6a). Further sub-analysis showed that both GORD (24%; $p<0.001$) and FH patients (33%; $p=0.010$) had fewer effective swallows than healthy subjects. In other words, there was an increased frequency of ineffective (simultaneous or wide breaks in peristalsis) and failed (< 3 cm contractility) swallows in both GORD and FH patients compared to normal volunteers. On the other hand, there was no significant difference in the frequency of effective swallows between the GORD and FH subgroups. ($p=0.211$) (Figure 6.6b).

There was a correlation in the number of effective swallows and the time required to consume the test meal (PC 0.476, $p=0.053$) (Figure 6.7). This was unlike healthy volunteers in whom there was no correlation (PC 0.351 $p=0.320$). (Chapter 5, Figure 5.12).

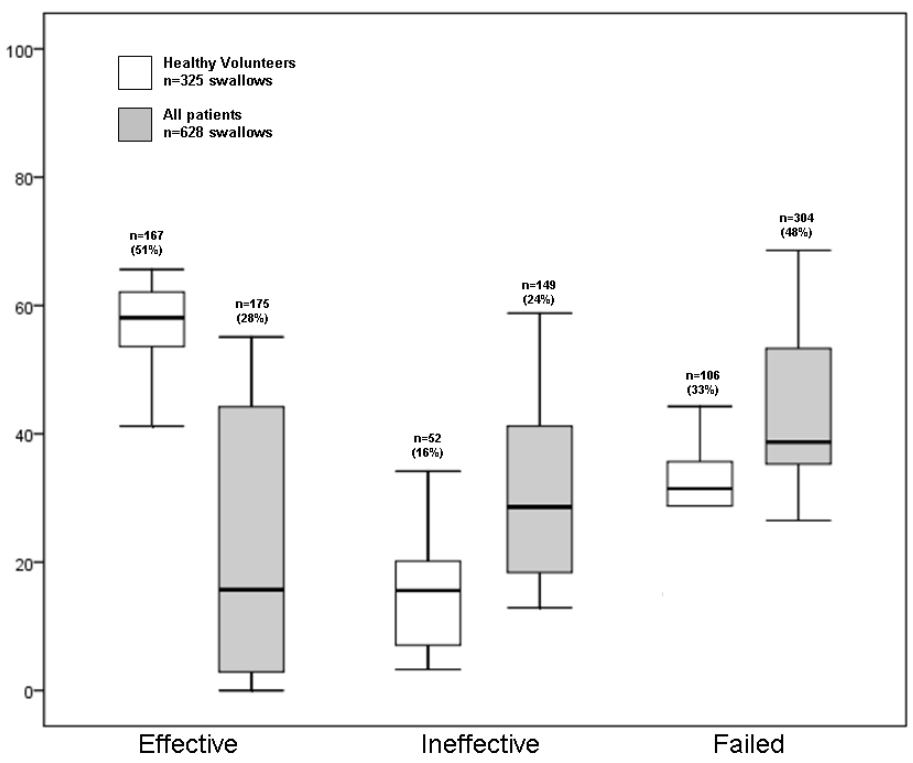


Figure 6.6a

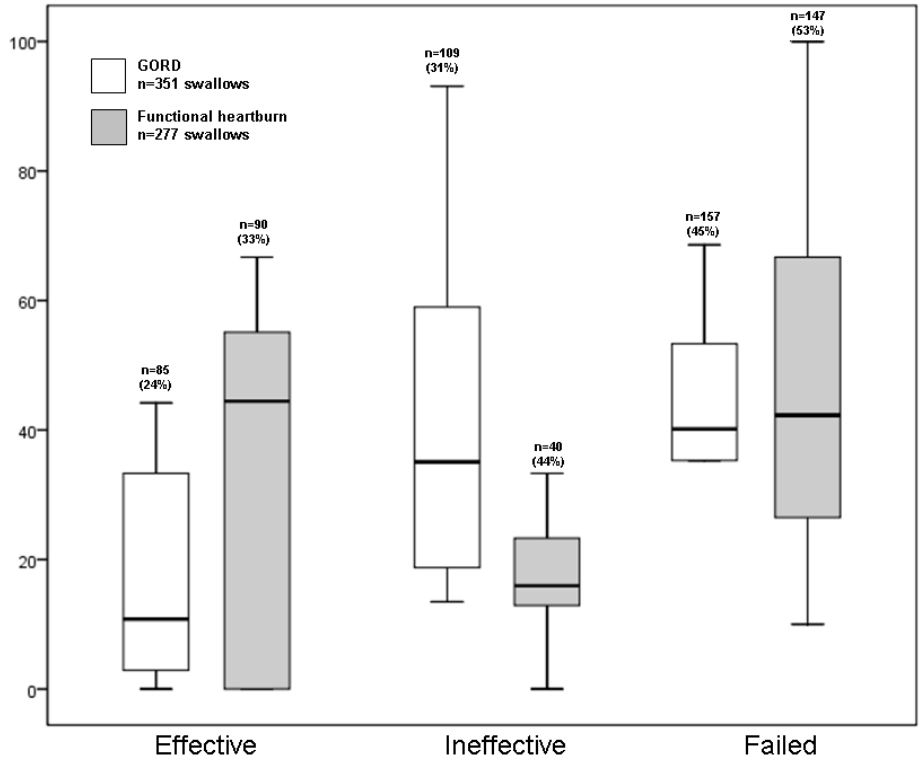


Figure 6.6b

Figure 6.6 Effectiveness of peristalsis box plot (a) The frequency of effective swallows during a standardised test meal was greater in healthy volunteers than patients overall ($p<0.001$). (b) There was no significant difference in the frequency of effective swallows between GORD and Functional Heartburn patients ($p=0.211$).

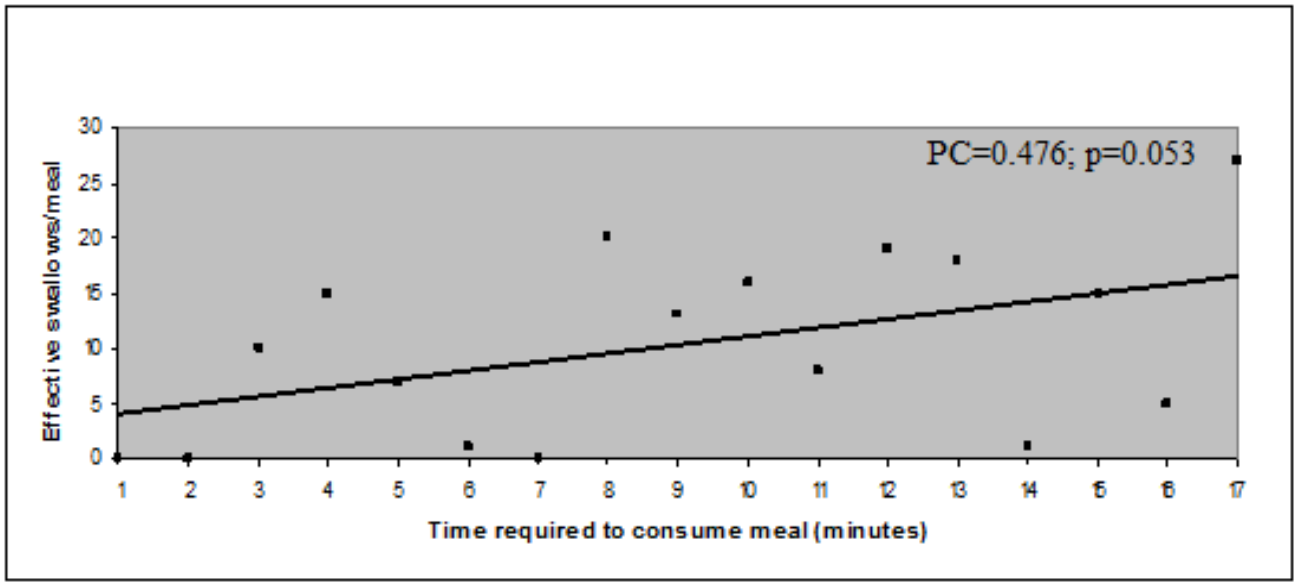


Figure 6.7 Frequency of effective swallows required to consume the test meal over time in patients overall (n=18) (PC = Pearson's correlation)

6.3.4 Multiple water swallows (MWS) in health and in patients **(Table 6.4)**

The overall number and duration of swallows required to freely drink 200ml of water was similar in healthy volunteers (n=10) and patients (n=18) (p=0.483 and 0.204 respectively). Compared to the GORD group (n=11), patients with FH (n=7) required a similar number of swallows (p=0.361) over the same duration (p=0.469). There was a (statistically) similar subjective measure of oesophageal contractile suppression (p=0.076); however although the median MWS contractility suppression score was '0' in the patient group, 5 exhibited complete suppression of contractility (score of '4'), suggesting resistance to flow at the level of the OGJ. Two of these comprised of patients with abnormal pH testing and may imply a peptic stricture (see discussion).

An effective post-MWS oesophageal contraction was seen in 80% of healthy subjects and 39% of patients (p=0.055). Further sub-analysis showed that an effective post-MWS oesophageal contraction was even less prevalent in patients with GORD (27%; p=0.030) although it was seen in just over half (57%) of those with FH (p=0.593); however the frequency of post-MWS oesophageal contractility between GORD and FH patients was statistically similar (p=0.332). There was no difference in the frequency of effective post-MWS LOS after-contraction between healthy volunteers and any of the subgroups (p>0.05 for all). All 7 FH patients and (6/11) 55% of the GORD sub-group had an effective post-MWS LOS contraction (p=0.101). (Table 6.4 and Figure 6.8)

There was no difference in the median number of swallows required to open the LOS (at 15mmHg) between healthy subjects and patients (median of 2 swallows for both; p=0.166). Patients with FH required a greater number of pharyngeal deglutitions (median 7 swallows) to open the LOS than healthy volunteers (p=0.014); however the maximum number of swallows required was 21 in FH compared to 5 swallows in healthy subjects. There was no difference in the LOS shortening distance nor the LOS pressure pre- and post-MWS between healthy volunteers and patients overall nor in the sub-analysis between GORD and FH (p>0.05 for all). Also the calculated volume of water for every swallow was similar across all groups (between 13.5 and 15.4 ml overall; p>0.05). (Table 6.5)

	Healthy (n=10)			All patients (n=18)				GORD (n=11)			FH (n=7)			
	Median (IQR)	5th %ile	95th %ile	Mean ±SE (SD)	Median (IQR)	Mean ±SE (SD)	p (Healthy vs patients)	Median (IQR)	Mean ±SE (SD)	p (Healthy vs GORD)	Median (IQR)	Mean ±SE (SD)	p (Healthy vs FH)	p (GORD vs FH)
MWS number of swallows	15.5 (11.8, 20.3)	10.5	23.8	16.3±1.1 (5.3)	14 (12.3,17.3)	14.5±0.9 (4.4)	0.483	13 (12.5,14.5)	13.6±0.6 (3.0)	0.304	14 (12.5,21.0)	15.9±1.2 (6.0)	1.000	0.361
MWS duration (s)	22 (19,29)	15	33	23±1 (7)	32 (17,44)	34±4 (20)	0.204	30 (17,37)	33±5 (22)	0.360	41 (23,49)	36±4 (17)	0.187	0.469
MWS suppression of contractility (0 - no contractions, 1 almost complete, 2 partial, 3 minimal, 4 no suppression)	0 (0.0,0.0)	0	0	0.0±0.0 (0.0)	0 (0,4.0)	1.4±0.4 (1.8)	0.022	0 (0.0,0.0)	0.8±0.4 (1.7)	0.146	2 (0.5,4.0)	2.1±0.4 (1.9)	0.002	0.076
Effective post MWS contraction	8/10	(80%)			7/18	(39%)	0.055	3/11	(27%)	0.030	4/7	(57%)	0.593	0.332
Effective post MWS LOS contraction	8/10	(80%)			14/18	(78%)	1.000	6/11	(55%)	0.362	7/7	(100%)	0.485	0.101

Table 6.4 Measurements of oesophageal function during and after multiple water swallows (MWS) for healthy subjects and all patients. Measurements are presented also from the secondary analysis of patients with and without an objective evidence of GORD (i.e. GORD vs. Functional Heartburn; FH)

Mann-Witney test was used to assess quantitative swallow parameters (number of swallows, duration, suppression of contractility) between groups (Healthy vs. Patients vs. GORD vs. FH). Fisher exact test was used to assess the difference in the frequency of effective/ineffective oesophageal and LOS aftercontraction between the groups.

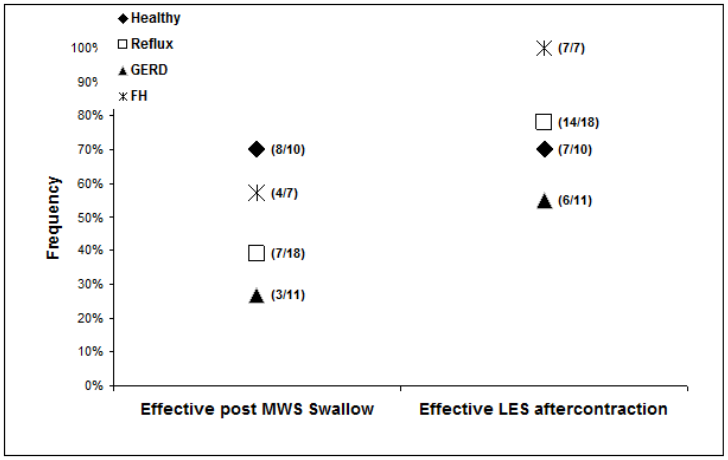


Figure 6.8 Frequency of post-MWS oesophageal and lower oesophageal sphincter contraction in healthy volunteers and patients as well as sub-group analysis of those with gastro-oesophageal reflux disease and Functional Heartburn (FH).

	Healthy (n=10)	All patients (n=18)		GORD (n=11)		FH (n=7)		
	Median (IQR)	Median (IQR)	p (patients)	Median (IQR)	p (GORD)	Median (IQR)	p (Healthy vs FH)	p (GORD vs FH)
Swallows until LOS relaxes (≤15mmHg)	2 (0,3)	2 (0,7)	0.166	1 (0,5)	0.873	7 (4,9)	0.014	0.092
Swallows until LOS relaxes (corrected to No of swallow %)	13% (0%,21%)	14% (0%,100%)	0.281	7% (0%,27%)	0.937	50% (18%,100%)	0.030	0.064
Time from start of MWS → LOS relaxation (s)	1.8 (0.0,2.8)	4.0 (0.0,17.0)	0.096	1.0 (0.0,13.5)	0.781	11.0 (5.0,22.5)	0.004	0.093
Time until LOS relaxes (≤15mmHg) (corrected to total time to complete the drink %)	8% (0%,14%)	17% (0%,100%)	0.137	6% (0%,19%)	0.751	40% (18%,100%)	0.014	0.072
LOS distance from pre→post MRS (cm)	0.3 (0.0,0.7)	0.9 (0.3,1.4)	0.099	1.1 (0.8,1.6)	0.047	0.3 (0.1,0.8)	0.688	0.110
MWS P difference pre and post MRS (mmHg)	7.6 (5.4,14.5)	11 (5.9,18.9)	0.350	11.2 (8.0,20.3)	0.171	7.2 (2.3,11.1)	0.841	0.157
Estimated volume per swallow (ml)	13.5 (9.9,17.2)	14.3 (11.7,16.3)	0.483	15.4 (13.8,16.0)	0.304	14.3 (9.5,16.2)	0.541	0.361
Estimated volume until LOS relaxes (ml)	25.6 (0.0,42.1)	28.6 (0.0,200.0)	0.281	13.3 (0.0,54.5)	0.937	100 (36.0,200.0)	0.228	0.064

Table 6.5 Secondary analysis results of MWS swallows for healthy subjects and patients as well as subgroup analysis for GORD and FH.

6.3.5 Dysmotility analysis

(Patients are identified by their initials)

Dysmotility - All patients (Table 6.6)

Hypo-contractility and aperistalsis were the most common dysmotility events seen with any swallow modality. Oesophageal spasm was not identified in any patient during water swallows although it was seen in 1 patient during bread swallows and in 2 additional patients with the test meal. Similarly, only 1 patient showed resistance to bolus passage at the LOS (raised IBP/IRP) during water swallows, while 2 new patients were found to have LOS obstruction during bread swallows and a further 2 during the test meal. One patient (RB) had an unstable LOS which was seen only during bread swallows and the test meal (see functional heartburn section 6.3.6 and Figure 6.9). On the other hand, among those with a change in manometry findings across modalities, 2 showed normalisation of peristalsis with solids from hypo-/aperistalsis with water swallows; one normalised initially with bread swallows and another during the test meal.

Overall, of the 18 patients studied, 4 showed a change in manometric diagnosis when progressing from water to bread swallows and 12 from water swallows to the test meal.

Dysmotility - GORD patients (Table 6.7)

5/11 patients with GORD had hypotensive dysmotility or aperistalsis during solid swallows (bread or test meal). Oesophageal spasm was identified in one patient following bread swallows and 2 further patients during the test meal. In one of these (JB) the trace was suggestive of diffuse oesophageal spasm (prolonged spasm of the distal segment) although this patient also had a raised IRP with water and solids. (patient JB Figure 6.10) In this case it is unclear which was the chief pathology; spasm may be a consequence of the distal obstruction to bolus passage or it may have been the primary problem which manifest only after adding work to the oesophagus. Three episodes of dysphagia associated with dysmotility were reproduced in this patient (see symptoms section 6.3.6 and Table 6.18).

Two other patients had hypotensive peristalsis during the test meal; the first (AA) had a very wide hiatus hernia of 7 cm (Figure 6.11), and the second (CG) was associated with an episode of retch/vomit when bolus transport was interrupted after an aperistalsis event (see symptoms section 6.3.6 and Table 6.18). In a final patient (MO) resistance to flow at the LOS was only revealed with the test meal.

In all, 8 patients had a change in manometry findings from water to solid swallows (bread or test meal), of which two showed normalisation of peristalsis with solids from hypo-/aperistalsis during water swallows (e.g. patient JL Figure 6.12).

Dysmotility - Functional heartburn patients (Table 6.8)

Of the 7 patients with functional heartburn, LOS obstruction was identified in 1 patient with bread swallows (patient CC Figure 6.13) and 2 further patients with the test meal (JW and IS). With JW (Figure 6.14), only aperistalsis was noted during water and bread swallows and no abnormality at the LOS was seen. (Water swallows IBP 7.1 mmHg and IRP 8.1 mmHg; Bread swallows IBP 10 mmHg and IRP 8.7 mmHg) With the test meal and during free drinking however, a non relaxing LOS became apparent (IBP 33.2 mmHg and IRP 26.6 mmHg) and was associated with pan-oesophageal pressurisation using the 30 mmHg isobaric contour. This was suggestive of achalasia. Manometry traces for IS are also shown in Figure 6.15. One patient's unstable LOS (patient RB Figure 6.9) only became apparent when swallowing solids. An unstable LOS was defined as a delayed LOS relaxation response to deglutition which may follow a brief period when the LOS does not relax; thus the 4 second IRP often remains normal, a relatively novel phenomenon. This patient was also found to have prolonged spasm activity following free drinking of 200 ml of water.

patient	dysmotility 5ml water	dysmotility 1cc bread	dysmotility meal
AA	normal/nondiagnostic	normal/nondiagnostic	hypo/aperistalsis
JB	resistance to flow at LOS	resistance to flow at LOS	oesophageal spasm
CG	normal/nondiagnostic	normal/nondiagnostic	hypo/aperistalsis
RH	hypo/aperistalsis	hypo/aperistalsis	oesophageal spasm
JJ	hypo/aperistalsis	hypo/aperistalsis	hypo/aperistalsis
JL	hypo/aperistalsis	hypo/aperistalsis	normal/nondiagnostic
SL	hypo/aperistalsis	normal/nondiagnostic	normal/nondiagnostic
MO	normal/nondiagnostic	normal/nondiagnostic	resistance to flow at LOS
DO	hypo/aperistalsis	hypo/aperistalsis	hypo/aperistalsis
MR	hypo/aperistalsis	oesophageal spasm	oesophageal spasm
TT	hypo/aperistalsis	hypo/aperistalsis	hypo/aperistalsis
RB	normal/nondiagnostic	unstable LOS	unstable LOS
CC	hypo/aperistalsis	resistance to flow at LOS	resistance to flow at LOS
SM	normal/nondiagnostic	normal/nondiagnostic	normal/nondiagnostic
DP	normal/nondiagnostic	normal/nondiagnostic	normal/nondiagnostic
IS	normal/nondiagnostic	normal/nondiagnostic	resistance to flow at LOS
KS	normal/nondiagnostic	normal/nondiagnostic	normal/nondiagnostic
JW	hypo/aperistalsis	hypo/aperistalsis	resistance to flow at LOS
	Number of patients with dysmotility		
	5ml water	1cc bread	meal
normal/nondiagnostic	8	8	5
hypo/aperistalsis	9	6	5
oesophageal spasm	0	1	3
resistance to flow at LOS	1	2	4
unstable LOS	0	1	1
	Number of patients with change in diagnosis		
	no change	water to bread	water to meal
	6	4	12
normalised from hypo/aperistalsis		1	2

Table 6.6 Distribution of dysmotility and change in HRM-based diagnosis in all patients (N=18). 4 and 12 patients had a different diagnosis from water to bread and test meal respectively. In two of these motility normalised with solid swallows.

patient	dysmotility 5ml water	dysmotility 1cc bread	dysmotility meal
AA	normal/nondiagnostic	normal/nondiagnostic	hypo/aperistalsis
JB	resistance to flow at LOS	resistance to flow at LOS	oesophageal spasm
CG	normal/nondiagnostic	normal/nondiagnostic	hypo/aperistalsis
RH	hypo/aperistalsis	hypo/aperistalsis	oesophageal spasm
JJ	hypo/aperistalsis	hypo/aperistalsis	hypo/aperistalsis
JL	hypo/aperistalsis	hypo/aperistalsis	normal/nondiagnostic
SL	hypo/aperistalsis	normal/nondiagnostic	normal/nondiagnostic
MO	normal/nondiagnostic	normal/nondiagnostic	resistance to flow at LOS
DO	hypo/aperistalsis	hypo/aperistalsis	hypo/aperistalsis
MR	hypo/aperistalsis	oesophageal spasm	oesophageal spasm
TT	hypo/aperistalsis	hypo/aperistalsis	hypo/aperistalsis

	Number of patients with dysmotility		
	5ml water	1cc bread	meal
normal/nondiagnostic	3	4	2
hypo/aperistalsis	7	5	5
oesophageal spasm	0	1	3
resistance to flow at LOS	1	1	1

	Number of patients with change in diagnosis		
	no change	water to bread	water to meal
	3	2	8
normalised from hypo/aperistalsis		1	2

Table 6.7 Distribution of dysmotility and change in HRM-based diagnosis in patients with evidence of GORD based on pH testing. (N=11)

patient	dysmotility 5ml water	dysmotility 1cc bread	dysmotility meal
RB	normal/nondiagnostic	unstable LOS	unstable LOS
CC	hypo/aperistalsis	resistance to flow at LOS	resistance to flow at LOS
SM	normal/nondiagnostic	normal/nondiagnostic	normal/nondiagnostic
DP	normal/nondiagnostic	normal/nondiagnostic	normal/nondiagnostic
IS	normal/nondiagnostic	normal/nondiagnostic	resistance to flow at LOS
KS	normal/nondiagnostic	normal/nondiagnostic	normal/nondiagnostic
JW	hypo/aperistalsis	hypo/aperistalsis	resistance to flow at LOS
	Number of patients with dysmotility		
	5ml water	**1cc bread**	**meal**
normal/nondiagnostic	5	4	3
hypo/aperistalsis	2	1	0
resistance to flow at LOS	0	1	3
unstable LOS	0	1	1
	Number of patients with change in diagnosis		
	no change	**water to bread**	**water to meal**
	3	2	4
normalised from hypo/aperistalsis		0	0

Table 6.8 Distribution of dysmotility and change in HRM-based diagnosis in patients with Functional Heartburn. (N=7)

6.3.6 Symptom analysis

(Patients are identified by their initials)

I. Water (5ml and MWS)

No symptoms were reproduced during 5 ml water swallows in any patient. 4/18 patients reported symptoms during or immediately after MWS: 1 x retch/vomit (CC), 2 x rumination (IS and DO) and 1 x belch during a prolonged transient relaxation of the LOS immediately after MWS (TT).

II. Bread (1cc)

All patients (Tables 6.9 and 6.10)

6/18 (33%) patients reported symptoms during the bread swallows (mean 2.2 symptom events; range 2-3). 5/18 (28%) patients overall, or 5/6 (83%) of those who were symptomatic, had at least one symptom event associated with oesophageal dysfunction (mean SAD 1.5 (range 0-2)). Overall, 3 events of raised IBP and 3 hypotensive manometric events preceded symptoms by ≤ 10 seconds. 1 patient who retched mid-procedure had no symptom association. Symptoms that were associated with dysmotility included: dysphagia (4 patients), retch/regurgitate (1 patient) and cough (1 patient). 4 of these patients had a D-SI of 100% (i.e. all symptoms were associated with dysfunction).

GORD patients (Tables 6.11 and 6.12)

Of the 11 patients with GORD, 3 (27%) reported symptoms during bread swallows; 2 with dysphagia (JB and DO) and 1 with cough (TT). All had an SAD of 2 with a D-SI of 100% with either hypo-peristalsis (n=2 events) or raised IBP (n=1 event) occurring prior to symptoms.

Functional heartburn patients (Tables 6.13 and 6.14)

Of the 7 patients with FH, 3 reported symptoms during bread swallows; 2 dysphagia (RB and CC) and 1 vomit/retching (KS). In RB and CC dysmotility events associated with symptoms were hypo-peristalsis (n=1) and raised IBP (n=2). One patient (RB) had a D-SI of 100% following 2 episodes of dysphagia and the other (CC) had a D-SI of 33% because 1 out of his 3 dysphagia events were associated with dysmotility.

Symptom	Total no. patients/symptom	%	Total no. symptoms	Total no. patients/SAD	Total no.SAD events/symptom
cough	1	17%	2	1	2
dysphagia	4	67%	9	4	7
retch/vomit	1	17%	2	0	0

Table 6.9 Total frequency of symptoms and Symptom-Associated Dysmotility (SAD) for all patients during bread swallows. (N=6)

Patient	Symptom	Total no. symptoms	SAD	D-SI	Dysmotility associated with symptom
TT	cough	2	2	100%	hypoperistalsis
RB	dysphagia	2	2	100%	1 x raised IBP &1 x hypoperistalsis
JB	dysphagia	2	2	100%	raised IBP
CC	dysphagia	3	1	33%	raised IBP
DO	dysphagia	2	2	100%	hypoperistalsis
KS	retch/vomit	2	0	0%	

Table 6.10 Reproduced symptoms, SAD (Symptom-associated dysmotility) and D-SI (Dysmotility-Symptom Index) for all patients during bread swallows. (N=6)

Symptom	Total no. patients/symptom	%	Total no. symptoms	Total no. patients/SAD	Total no.SAD events/symptom
dysphagia	2	67%	4	2	4
cough	1	33%	2	1	2

Table 6.11 Total frequency of symptoms and Symptom-Associated Dysmotility (SAD) for all GORD patients during bread swallows. (N=3)

Patient	Symptom	Total no. symptoms	SAD	D-SI	Dysmotility associated with symptom
TT	cough	2	2	100%	hypoperistalsis
JB	dysphagia	2	2	100%	raised IBP
DO	dysphagia	2	2	100%	hypoperistalsis

Table 6.12 Reproduced symptoms, SAD (Symptom-Associated Dysmotility) and D-SI (Dysmotility-Symptom Index) for all GORD patients during bread swallows (N=3)

Symptom	Total no. patients/symptom	%	Total no. symptoms	Total no. patients/SAD	Total no.SAD events/symptom
dysphagia	2	67%	5	2	3
retch/vomit	1	33%	2	0	0

Table 6.13 Total frequency of symptoms and Symptom-Associated Dysmotility (SAD) for all Functional heartburn patients during bread swallows. (N=3)

Patient	Symptom	Total no. symptoms	SAD	D-SI	Dysmotility associated with symptom
RB	dysphagia	2	2	100%	1 x raised IBP & 1 x hypoperistalsis
CC	dysphagia	3	1	33%	raised IBP
KS	retch/vomit	2	0	0%	

Table 6.14 Reproduced symptoms, SAD (Symptom-Associated Dysmotility) and D-SI (Dysmotility-Symptom Index) for all Functional heartburn patients during bread swallows. (N=3)

III. Meal

All patients* (*Tables 6.15 and 6.16)

12/18 (67%) patients reported symptoms during the test meal (mean 2.3 symptom events, range 0-10). 9/18 (50%) patients overall, or 9/12 (75%) of those who exhibited symptoms, had at least one symptom event which followed oesophageal dysfunction (mean SAD 1.8 (range 0-7)). Symptoms that were associated with dysmotility included: dysphagia/food sticking (3 patients), retch/regurgitation (2 patients), chest pain (1 patients), belch (1 patients) and cough (2 patients). Manometric dysmotility events that preceded symptoms by ≤10 seconds were: hypo-/aperistalsis (ineffective or failed peristalsis; n=6), oesophageal spasm (n=3), hypertensive peristalsis (n=1), outflow obstruction (n=1) and TLOSR with belching (n=1). Three patients with cough had no symptom association. 7/9 (78%) patients had a D-SI of 100% (i.e. all symptoms associated with dysfunction).

GORD patients (Tables 6.17 and 6.18)

Of the 11 patients with GORD, 7 (63%) patients reported symptoms during the test meal (mean 1.1 symptom events, range 0-3) with a mean SAD of 1.1 (range 0-3). Abnormal pressure events associated with symptoms were: hypo-/aperistalsis, hypertensive peristalsis and segmental spasm. Four patients had a D-SI of 100% (dysphagia, cough, chest pain and vomiting), one had a D-SI of 67% (retch/vomiting) and two had no association of symptoms with dysmotility (both cough).

Functional heartburn patients (Tables 6.19 and 6.20)

Of the 7 patients with FH, 5 (71%) patients reported symptoms during the test meal (mean 3.4 symptom events, range 1-10) with a median SAD of 3 (range 0-7). Dysmotility associated with symptoms were: pan-oesophageal pressurization, increased intra-bolus pressure, hypo-/aperistalsis and TLOSR. Three had a D-SI of 100% (dysphagia described as food sticking/difficulty swallowing, cough and painful belch), one had a D-SI of 70% (dysphagia followed by regurgitation) and one had no association with abnormal pressure events (cough).

Symptom	Total no. patients/symptom	%	Total no. symptoms	Total no. patients/SAD	Total no.SAD events/symptom
cough	5	42%	6	2	3
dysphagia	3	25%	16	3	13
retch/vomit	2	17%	4	2	3
chest pain	1	8%	1	1	1
belch	1	8%	1	1	1

Table 6.15 Total frequency of symptoms and Symptom-Associated Dysmotility (SAD) for all patients during the test meal (N=12)

Patient	Symptom	Total no. symptoms	SAD	D-SI	Dysmotility associated with symptom
CC	cough	2	2	100%	1 x raised IBP & 1 x aperistalsis
RH	cough	1	1	100%	segmental spasm
SL	cough	1	0	0%	
DP	cough	1	0	0%	
TT	cough	1	0	0%	
JB	dysphagia	3	3	100%	2 x spasm & 1 x hypertensive peristalsis
KS	dysphagia	10	7	70%	hypoperistalsis
JW	dysphagia	3	3	100%	PeP
DO	retch/vomit	3	2	67%	1 x hypoperistalsis & 1 x aperistalsis
CG	retch/vomit	1	1	100%	aperistalsis
JJ	chest pain	1	1	100%	aperistalsis
RB	belch	1	1	100%	TLOSR

Table 6.16 Reproduced symptoms, SAD (Symptom-Associated Dysmotility) and D-SI (Dysmotility-Symptom Index) for all patients during the test meal (N=12)

(IBP = Intra-bolus pressure; PeP = Pan-oesophageal pressurisation; TLOSR = Transient Lower Oesophageal Sphincter Relaxation)

Symptom	Total no. patients/symptom	%	Total no. symptoms	Total no. patients/SAD	Total no.SAD events/symptom
cough	3	43%	3	1	1
dysphagia	1	14%	3	1	3
retch/vomit	2	29%	4	2	3
chest pain	1	14%	1	1	1

Table 6.17 Total frequency of symptoms and Symptom-Associated Dysmotility (SAD) for all GORD patients during the test meal (N=7)

Patient	Symptom	Total no. symptoms	SAD	D-SI	Dysmotility associated with symptom
RH	cough	1	1	100%	segmental spasm
SL	cough	1	0	0%	
TT	cough	1	0	0%	
JB	dysphagia	3	3	100%	2 x spasm & 1 x hypertensive peristalsis
DO	retch/vomit	3	2	67%	1 x hypoperistalsis & 1 x aperistalsis
CG	retch/vomit	1	1	100%	aperistalsis
JJ	chest pain	1	1	100%	aperistalsis

Table 6.18 Reproduced symptoms, SAD (Symptom-Associated Dysmotility) and D-SI (Dysmotility-Symptom Index) for all GORD patients during the test meal (N=7)

Symptom	Total no. patients/symptom	%	Total no. symptoms	Total no. patients/SAD	Total no.SAD events/symptom
cough	2	40%	3	1	2
dysphagia	2	40%	13	2	10
belch	1	20%	1	1	1

Table 6.19 Total frequency of symptoms and Symptom-Associated Dysmotility (SAD) for all Functional Heartburn patients during the test meal (N=5)

Patient	Symptom	Total no. symptoms	SAD	D-SI	Dysmotility associated with symptom
CC	cough	2	2	100%	1 x raised IBP & 1 x aperistalsis
DP	cough	1	0	0%	
KS	dysphagia	10	7	70%	hypoperistalsis
JW	dysphagia	3	3	100%	PeP
RB	belch	1	1	100%	TLOSR

Table 6.20 Reproduced symptoms, SAD (Symptom-Associated Dysmotility) and D-SI (Dysmotility-Symptom Index) for all Functional Heartburn patients during the test meal (N=5)

(IBP = Intra-bolus pressure; PeP = Pan-oesophageal pressurisation; TLOSR = Transient Lower Oesophageal Sphincter Relaxation)

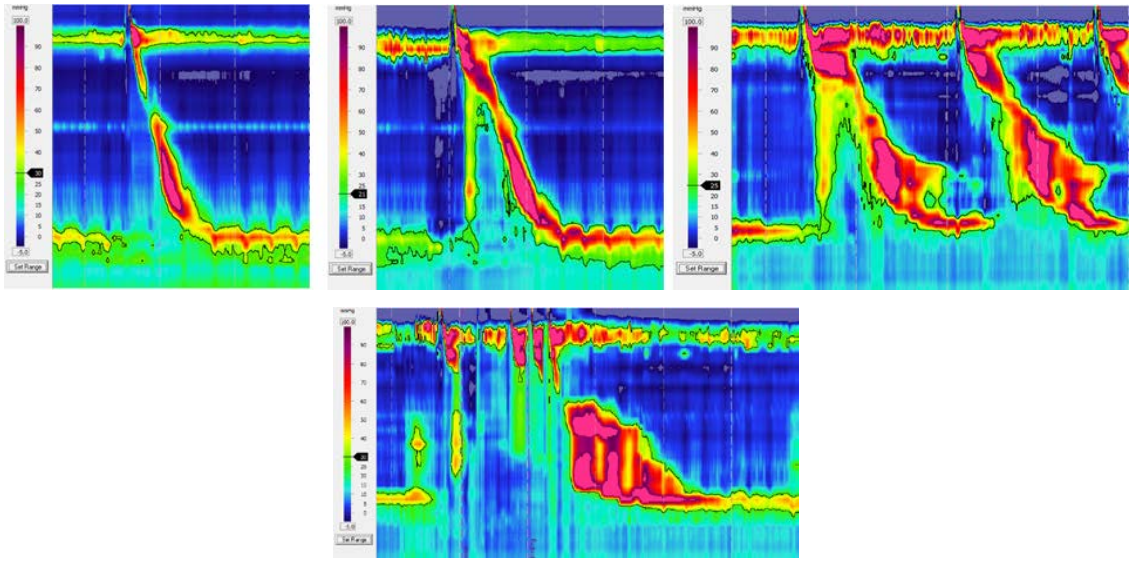


Figure 6.9 Patient RB. 35 year old female with globus and dysphagia to dry foods for which she often needed to drink water. She also complained of heartburn and acid-like regurgitation which reached the pharynx and was associated with chest pain. Symptoms occurred during the day and night. Twice daily lansoprazole reduced the heartburn but not the dysphagia or regurgitation. Gastroscopy was normal and 24 hour pH monitoring showed no evidence of GORD or reflux-symptom association.

Left panel: Normal 5ml water swallow. Middle and right panels: Although 1cc bread swallows and test meal showed a normal overall pressure gradient, on closer scrutiny there was an initial rise in IBP (up to 20 mmHg during bread swallows and 26 mmHg during the meal) followed by a sudden drop during which time the bolus would pass. This implies poor compliance of the LOS rather than a fixed obstruction. There was 100% association (D-SI) with dysphagia during bread swallows. Bottom panel: During the post-meal observation period and after drinking water, there was a prolonged high pressure event in the distal segment of the oesophagus during the clearance phase. This was suggestive of diffuse oesophageal spasm although no symptoms were reproduced.

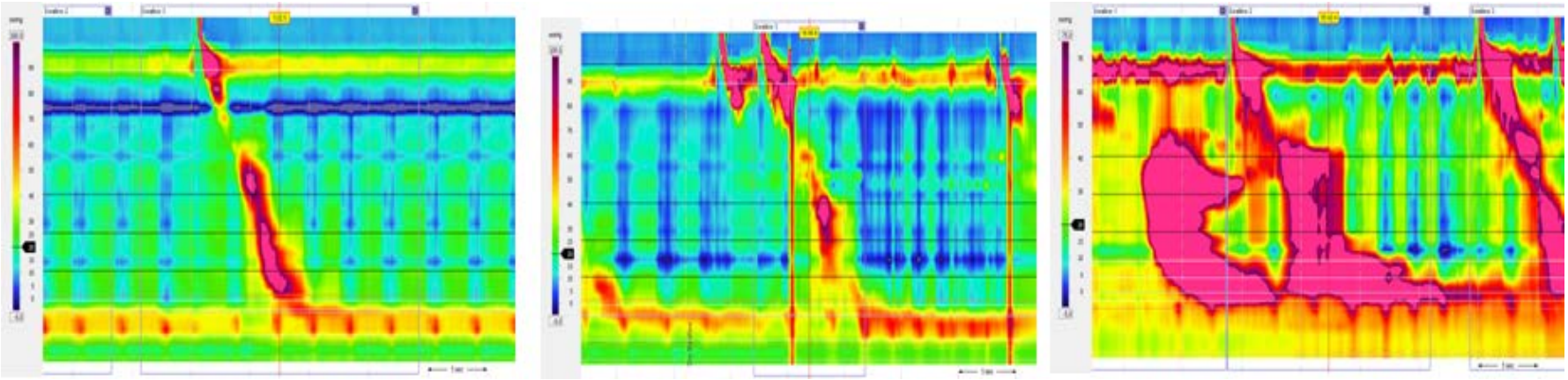


Figure 6.10 Patient JB. 49 year old female with a daily sensation of food sticking in the proximal oesophagus as well as nocturnal regurgitation and heartburn. Acid-reducing medication did not improve her symptoms. Endoscopy was normal. 24 hour pH study was pathological for all reflux parameters: Total reflux (7.0%), Upright reflux (8.7%) and Supine reflux (5.9%). DeMeester score was 35.8 (normal <14.72). Symptom Index for regurgitation was 100% (positive >50%).

Left panel: 5 ml water swallow was normal showing an effective well-coordinated peristalsis. Visually there was a recurrent and pronounced inspiratory diaphragmatic pinch at the LOS. Although the IBP was raised (23.6 mmHg) the mean IRP was normal (15.5 mmHg) which implied that the bolus passed through the LOS normally. No symptoms were reproduced and the patient was well throughout.

Middle panel: 1 cc bread swallow also showed a raised IBP (32.1 mmHg) with normal mean IRP (15.1 mmHg), but now intermittent focal segmental spasms began to appear. Two episodes of dysphagia coincided with dysmotility (D-SI 100%).

Right panel: Standardised meal showed clear evidence of obstruction with a raised IBP (55.3 mmHg) and an IRP (21 mmHg). All 3 episodes of dysphagia coincided with dysmotility (D-SI 100%). The symptomatic resistance to flow at the OGJ combined with positive ambulatory pH studies were suggestive of a peptic stricture at the OGJ secondary to chronic reflux.

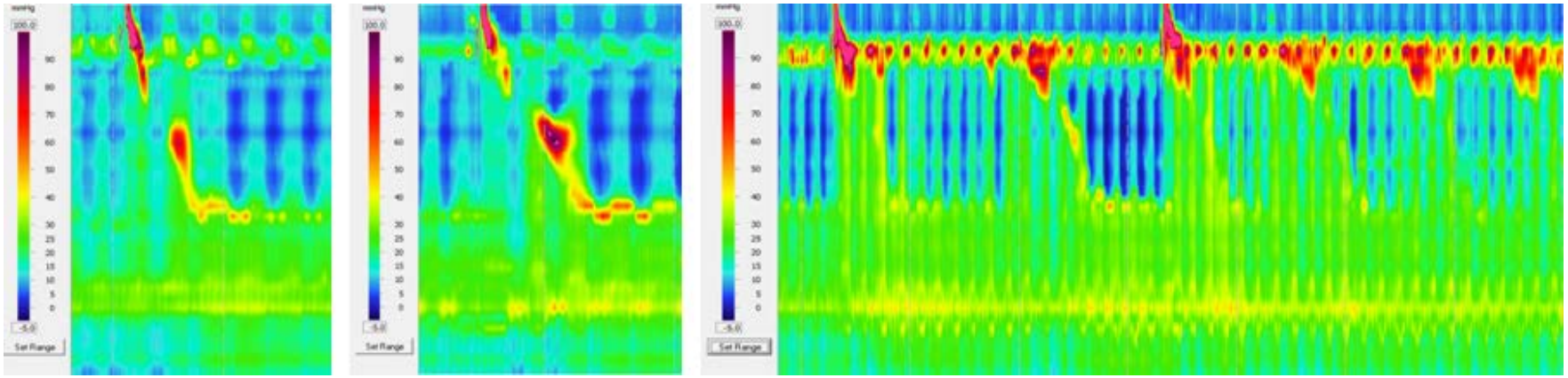


Figure 6.11 Patient AA. 75 year old lady who presented with a 4 year history of daytime and nocturnal heartburn, regurgitation and central burning chest pain. Intermittent Nexium, Gaviscon and Domperidone helped briefly. Endoscopy was normal. 24 hour pH study was pathological for all reflux parameters: Total reflux (38.0%), Upright reflux (38.0%), Supine reflux (38.2%). DeMeester score was 145 (normal <14.72). Symptom index for heartburn was 100%.

Left panel: 5ml water swallows were normal although a wide (6.4 cm) hiatus hernia was visible.

Middle panel: 1 cc bread swallows showed normal peristalsis, again with a very wide (8.3 cm) hiatus hernia.

Right panel: Test meal showed that only 1 (6%) of the 17 swallows was effective, with the majority (59%) showing hypotensive contractility and the rest showing failed dysmotility.

During the post meal observation there were 4 episodes of spontaneous LOS relaxations and 3 episodes of gradual drift of the LOS to a pressure of 0 lasting an average of 41 seconds. The hypotensive dysmotility was apparent only during the test meal and was likely a consequence of severe chronic reflux.

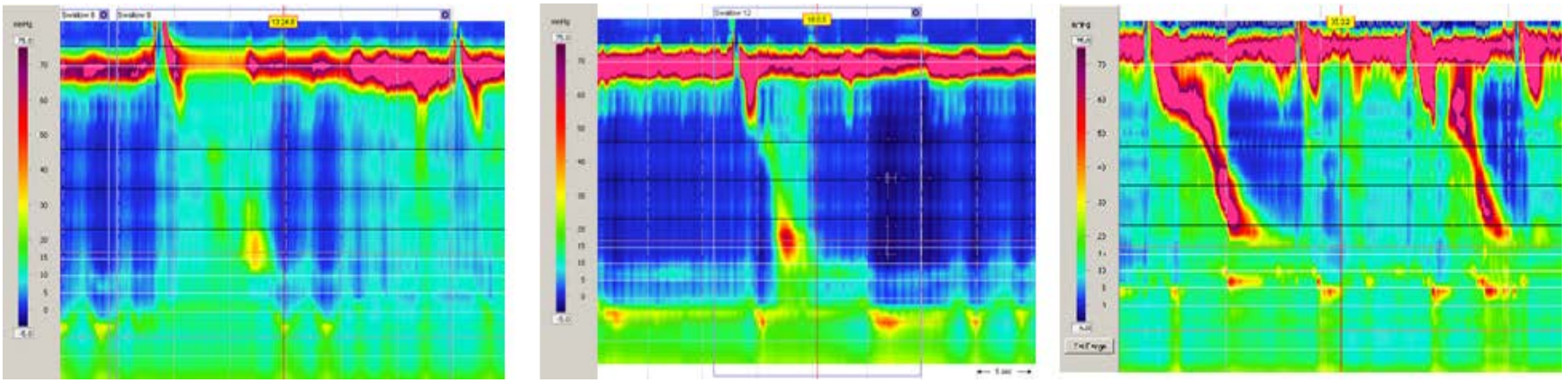


Figure 6.12 Patient JL. 55 year old male presented with the sensation of food sticking in the mid-oesophagus (requiring large amounts of water to pass) as well as a central burning chest pain and regurgitation. Omeprazole relieved the burning chest pain and dysphagia but not the regurgitation. Endoscopy showed grade A oesophagitis and the possibly a small hiatus hernia. 24 hour pH study showed evidence of oesophageal acid exposure for all parameters: Total Reflux (11.1%), Upright Reflux (11.8%) and Supine Reflux (10.4%) reflux. DeMeester score was 46.3 (normal <14.72). Symptom index for heartburn was 80% (positive >50%).

Left panel: 5 ml water swallows showed absent or hypotensive peristaltic activity.

Middle panel: 1cc bread swallows showed hypotensive peristalsis and a 1.7 cm hiatus hernia became apparent.

Right panel: Test meal showed that peristalsis activity normalised during 1/3 of swallows and a 2-3 cm hiatus hernia became evident.

Post-meal observation (see Figure 6.16) showed 11 LOS relaxation (LOSR) events, 9 of which were associated with a common cavity (i.e. reflux). Half of the LOSR events coincided with belch and 2 with rumination events. Also 3 episodes of LOS drift (to a pressure of 0) occurred; mean length of time of 28 seconds during the 10 minute observation period.

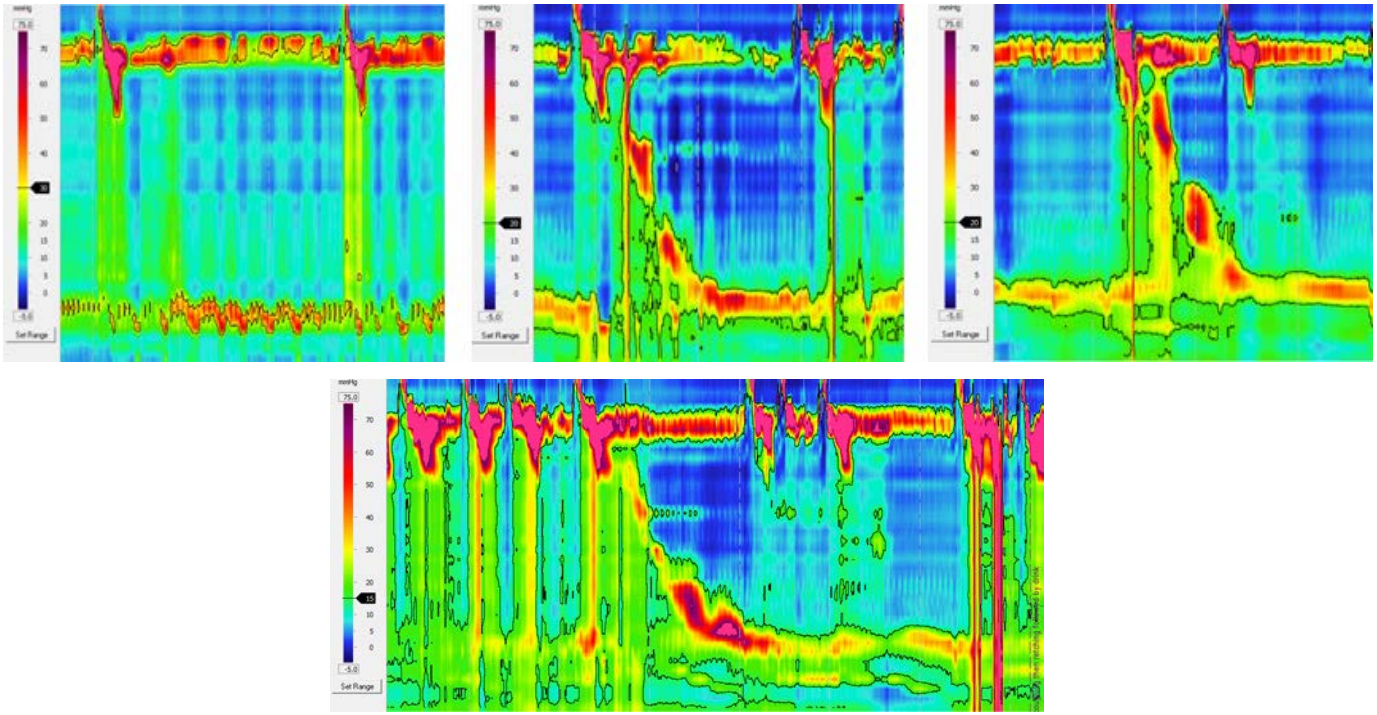


Figure 6.13 Patient CC. 63 year old lady with a daily sensation of food sticking in the mid-oesophagus often followed by cough and then food regurgitation. She also complained of heartburn when lying flat. Barium swallow only showed a hiatus hernia. Endoscopy was normal. Once daily Nexium helped with heartburn but not the dysphagia, cough or regurgitation. 24 hour pH study showed no reflux.

Left panel: Aperistalsis (no contractility within the 30 mmHg isobaric contour) was seen with any 5ml water swallow. Middle and right panels: Bread and standardised meal showed resistance to flow at the OGJ with a raised IRP (18 mmHg) and IBP (24 mmHg). Cough/regurgitation was associated with dysmotility and resistance to flow (D-SI 100%). Bottom panel: free drinking elicited clearly the LOS obstruction which was followed by excessive coughing and retching because of un-cleared oesophageal contents.

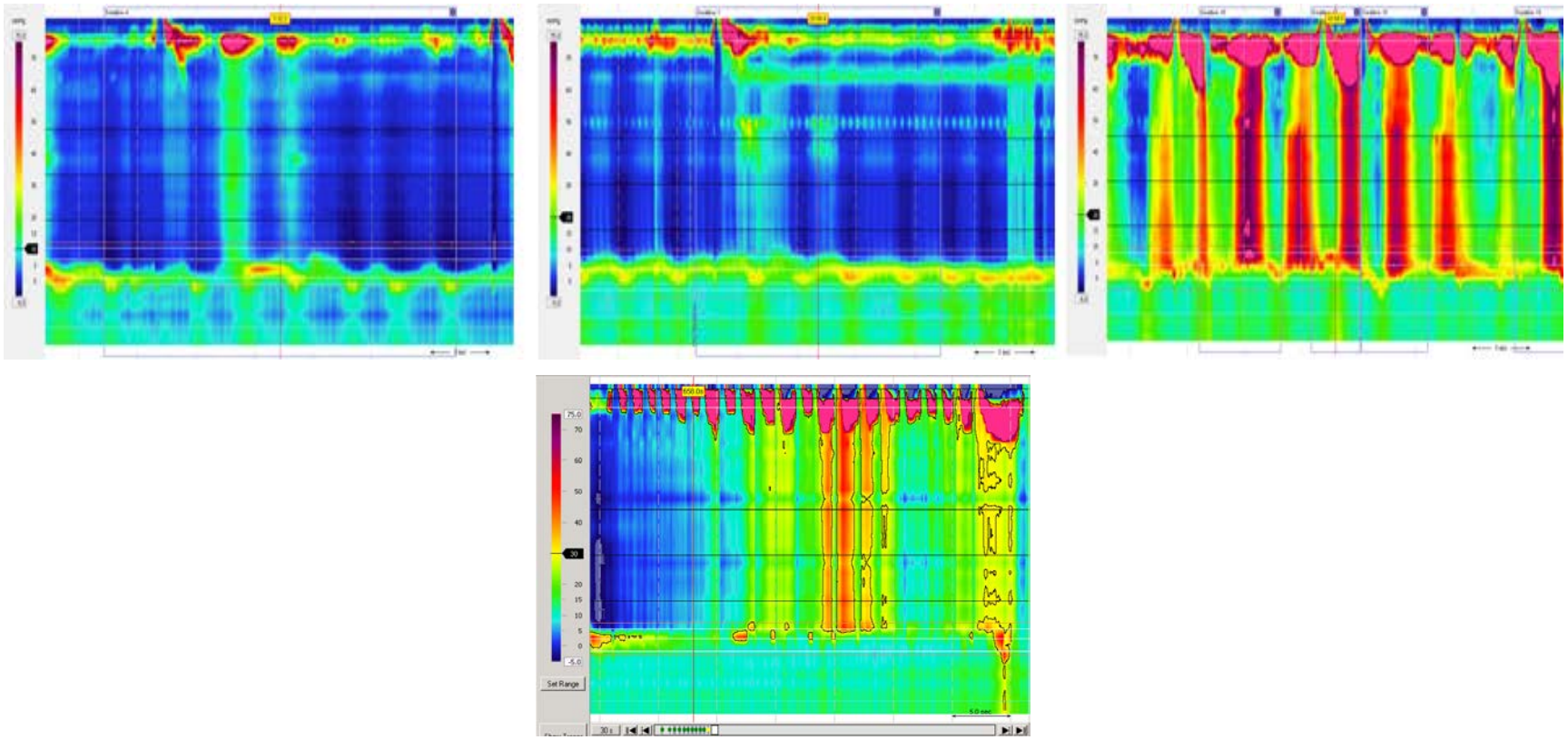


Figure 6.14 Patient JW. 66 year old lady presented with a 7 year history of dysphagia and chest pain up to 2-3 times per week. Symptoms were especially worse when supine. Drinking water did not help. Symptoms improved with Lansoprazole 30 mg and post-meal Gaviscon. Endoscopy was non-diagnostic. 24 hour pH study was normal.

Figure 6.14 (continued). Left and middle panels: water and bread swallows were aperistaltic (no contractility seen within the 30 mmHg isocontour). LOS basal tone (18.2 mmHg), IRP (8.1 mmHg) and IBP (7.1 mmHg) were normal. No symptoms were reproduced.

Right panel: Standardised meal showed a non-relaxing LOS with a raised IRP (26.6 mmHg) and IBP (33.2 mmHg) as well as pan-oesophageal pressurisation with an isobaric contour of greater than 30 mmHg. Dysphagia was reproduced from the mid-point of the meal with every swallow.

Bottom panel: 200ml multiple water swallow confirmed a non-relaxing LOS with resistance to flow and pan-oesophageal pressurisation. Achalasia (non-relaxing LOS and aperistalsis) was only confirmed with solid swallows and free drinking.

The Chicago classification,[118,125] which is based on water swallows alone, would define this as Type I (Classical achalasia); however it is more likely that this patient had pan-oesophageal pressurisation (pathognomic for Type II achalasia) which manifest only during free drinking and test meal. As described in the Chapter 1, Type II achalasia has a better prognosis than Type I (especially to myotomy) if treated early, and is theorised to be a pre-cursor to Classical achalasia.[136]

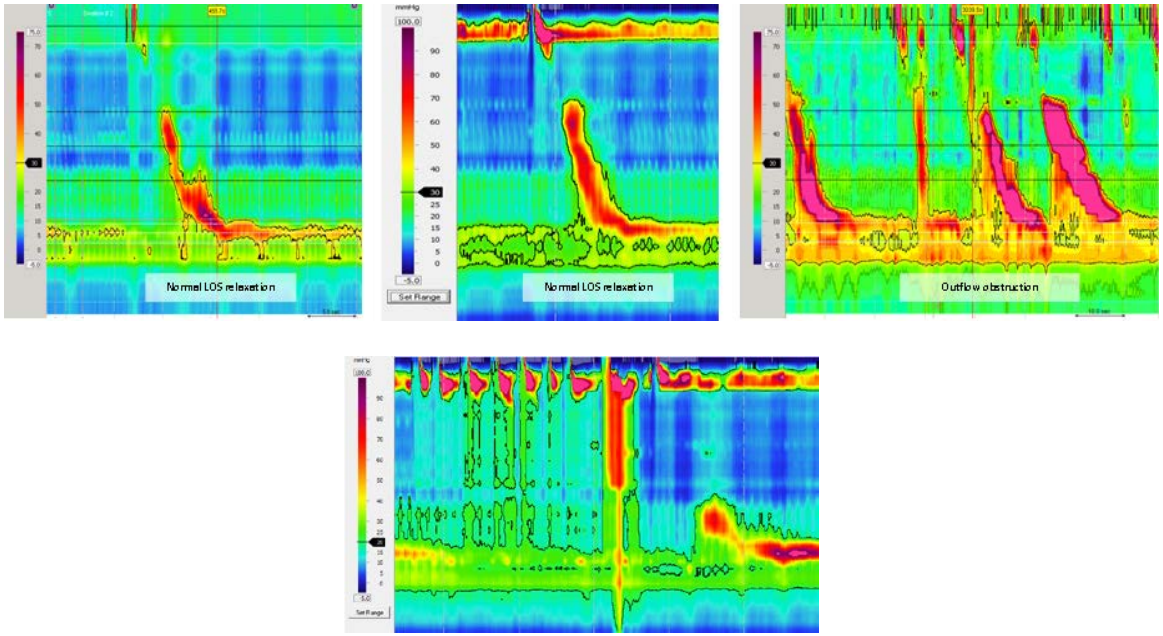


Figure 6.15 Patient IS. 72 year old lady presented with over 10 year history of heartburn refractory to low dose once daily Lansoprazole. Symptoms were worst after meals, although they could also recur at night. Endoscopy and 24 hour pH study was normal.

Left and middle panels: 5ml water and bread swallows were normal.

Right panel: Standardised meal showed evidence of resistance to flow with a raised IRP of 20 mmHg and IBP of 26.2 mmHg. There was also the sensation of food sticking in the oesophagus towards the end of the meal and the beginning of the observation period; however this occurred out-with the 10 second interval limit required for a D-SI calculation.

Bottom panel: Free drinking showed evidence of resistance to flow at the OGJ. This LOS outflow obstruction only manifest during the test meal and free drinking.

6.3.7 Post-meal observation (Table 6.21 and 6.22)

16 patients completed the 10 minute post-prandial observation period. Compared to the 10 healthy controls, patients had similar numbers of LOS sphincter relaxations, common cavity events and associated symptoms (belching or chest pain) overall. Secondary analysis of patients with GORD showed a higher number of swallow-associated LOS relaxations (SLOSRs) with and without common cavity events (2.5 (1.3,4.0)) compared to healthy subjects (1.0 (0.0,1.0); p=0.019) and FH patients (1.0 (0.3,1.0); 0.019 respectively). (Table 6.21) A gradual LOS drift with loss of pressure over >10 seconds but no common cavity was seen in 3/10 healthy volunteers (median 15 seconds) and 3/16 patients (all GORD; median 28 seconds). Data for every healthy volunteer and patient is presented in Table 6.21. A representative trace of the post-prandial period is presented in Figure 6.16 (patient JL).

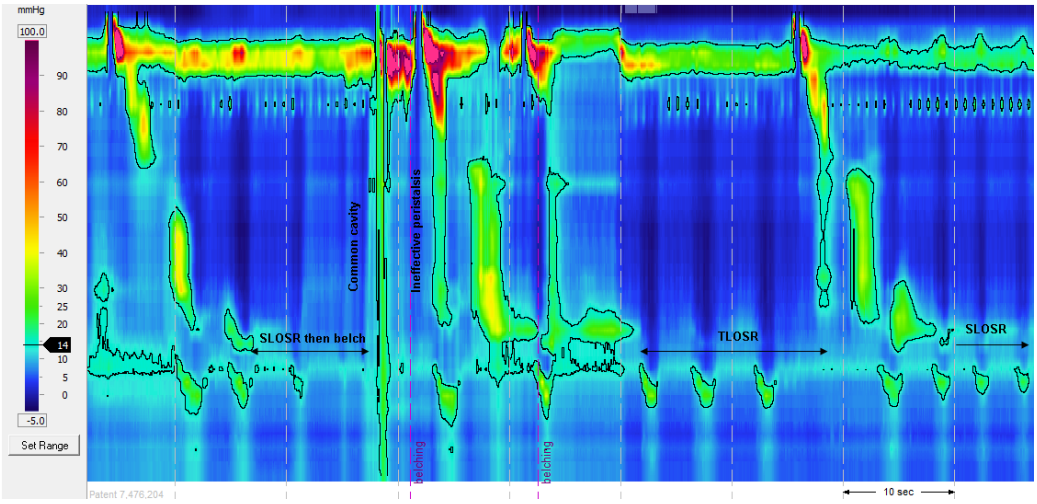


Figure 6.16 HRM snapshot of the post-meal observation in patient JL showing 2 x SLOSR, 1 x TLOSR and 2 x belch events one of which was associated with a common cavity event. An attempt at swallowing the refluxate after the first SLOSR was unsuccessful. This patient had evidence of severe GORD on pH studies.
(See Figure 6.12 for details of patient JL)

	Healthy (n=10)	All patients (n=16)	GORD (n=10)	FH (n=6)	p (healthy vs patients)	p (healthy vs GORD)	p (healthy vs FH)	p (GORD vs FH)
TLOSR	2.0 (2.0,3.5)	2.0 (1.0,3.0)	2.0 (1.0,2.8)	1.5 (0.3,2.8)	0.340	0.525	0.287	0.470
TLOSR + CC	2.0 (1.3,3.5)	1.5 (1.0,3.0)	1.5 (1.0,2.8)	1.5 (0.3,2.8)	0.255	0.366	0.290	0.655
SLOSR	1.0 (0.0,1.8)	1.0 (1.0,3.3)	2.5 (1.3,4.8)	1.0 (1.0,1.0)	0.098	0.019	0.953	0.009
SLOSR + CC	1.0 (0.0,1.0)	1.0 (1.0,3.3)	2.5 (1.3,4.0)	1.0 (0.3,1.0)	0.118	0.019	0.811	0.019
Total LOSR	3.5 (2.3,4.8)	4.0 (2.8,5.3)	4.5 (3.3,6.8)	2.5 (1.3,3.0)	0.650	0.145	0.247	0.049
Total LOSR + CC	3.0 (2.0,4.0)	3.0 (2.8,5.0)	4.5 (3.0,5.8)	2.5 (1.3,3.0)	0.610	0.124	0.240	0.036

Table 6.21 Post-meal observation for healthy subjects (n=10), all patients (n=16) as well as sub-analysis of patients with pH evidence of GORD (n=10) and with Functional Heartburn (FH; n=6). Parameters are presented as median (IQR).

(TLOSR = Transient lower oesophageal sphincter relaxation. SLOSR = Swallow-related lower oesophageal sphincter relaxation. CC = common cavity)

	TLOSR	TLOSR + CC	TLOSR + belch	SLOSR	SLOSR + CC	SLOSR + belch	LOSR ALL	LOSR + CC	LOSR + belch	LOS drift then loss of LOS (total number)	LOS drift then loss of LOS (total time - seconds)
JA	4	4	4	2	2	2	6	6	6	0	
DB	1	1	1	3	3	3	4	4	4	0	
AF	4	4	4	0	0	0	4	4	4	0	
SH	5	4	4	0	0	0	5	4	4	0	
MM	2	2	1	1	1	1	3	3	2	0	
SM	2	1	0	1	1	1	3	2	1	3	25
RN	1	1	1	1	1	1	2	2	2	0	
SP	2	2	1	3	1	1	5	3	2	1	14
SR	2	2	0	0	0	0	2	2	0	5	15
SS	2	2	2	0	0	0	2	2	2	0	

Table 6.22a Healthy subjects

	TLOSR	TLOSR + CC	TLOSR + symptoms	SLOSR	SLOSR + CC	SLOSR + symptoms	LOSR ALL	LOSR + CC	LOSR + symptoms	LOS drift then loss of LOS (total number)	LOS drift then loss of LOS (total time - seconds)
AA	3	3	3	1	1	0	4	4	3	3	41
RB	3	3	3	1	1	1	4	4	4	0	
JB	1	1	1	1	0	0	2	1	0	0	
CG	1	1	0	2	2	1	3	3	1	0	
RH	4	4	2	1	1	0	5	5	2	4	13
JL	5	3	1	6	6	4	11	9	5	3	28
SL	2	2	1	4	4	4	6	6	5	0	
SM	1	1	1	1	1	1	2	2	2	0	
MO	1	1	1	2	2	0	3	3	2	0	
DO	2	1	0	5	4	2	7	5	2	0	
DP	0	0	0	1	1	0	1	1	0	0	
MR	2	2	2	5	5	5	7	7	7	0	
IS	2	2	2	1	1	1	3	3	3	0	
KS	4	3	2	1	0	0	5	3	2	0	
TT	1	0	0	3	3	3	4	3	3	0	
JW	0	0	0	0	0	0	0	0	0	0	

Table 6.22b All patients

	TLOSR	TLOSR + CC	TLOSR + symptoms	SLOSR	SLOSR + CC	SLOSR + symptoms	LOSR ALL	LOSR + CC	LOSR + symptoms	LOS drift then loss of LOS (total number)	LOS drift then loss of LOS (total time - seconds)
AA	3	3	3	1	1	0	4	4	3	3	41
JB	1	1	1	1	0	0	2	1	0	0	
CG	1	1	0	2	2	1	3	3	1	0	
RH	4	4	2	1	1	0	5	5	2	4	13
JL	5	3	1	6	6	4	11	9	5	3	28
SL	2	2	1	4	4	4	6	6	5	0	
MO	1	1	1	2	2	0	3	3	2	0	
DO	2	1	0	5	4	2	7	5	2	0	
MR	2	2	2	5	5	5	7	7	7	0	
TT	1	0	0	3	3	3	4	3	3	0	

Table 6.22c Gastro-oesophageal reflux disease (GORD)

	TLOSR	TLOSR + CC	TLOSR + symptoms	SLOSR	SLOSR + CC	SLOSR + symptoms	LOSR ALL	LOSR + CC	LOSR + symptoms	LOS drift then loss of LOS (total number)	LOS drift then loss of LOS (total time - seconds)
RB	3	3	3	1	1	1	4	4	4	0	
SM	1	1	1	1	1	1	2	2	2	0	
DP	0	0	0	1	1	0	1	1	0	0	
IS	2	2	2	1	1	1	3	3	3	0	
KS	4	3	2	1	0	0	5	3	2	0	
JW	0	0	0	0	0	0	0	0	0	0	

Table 6.22d Functional heartburn (FH)

Table 6.22 TLOSR, SLOSR, CC and LOS drift during post-meal observation. Distribution of transient (TLOSR), swallow-associated (SLOSR) and combined (LOSR) lower oesophageal relaxations with/without common cavity (CC) and belch and the frequency and time the LOS drifts to a pressure of zero. Results are shown for every (a) healthy volunteer and (b) patient as well as a sub-analysis of patients with (c) GORD and (d) FH.

6.3.8 Final diagnosis and clinical outcome

Management decisions were made by the referring physician/surgeon based on physiological challenge swallows (5ml water, 1cc bread, MWS, test meal, post-prandial observation) and ambulatory pH monitoring presented in the final report.

GORD patients

Of the 11 patients with GORD on pH-studies, 5 underwent anti-reflux surgery (assessed 9-48 months after surgery) and all reported excellent functional outcome. 3 of these patients (RH, JL, TT) had a pathological oesophageal acid exposure with a raised Total reflux (TR 25%, 11% and 9.3% respectively) and reflux-symptom association (all SI for HB > 70%). On manometry all 3 had evidence of hypomotility, RH also exhibited episodes of focal spasm with the meal and both RH and TT had a D-SI of 100% for cough. Furthermore both RH and JL had >3 episodes of prolonged LOS drift to 0 mmHg (mean 13 and 28 seconds respectively) and JL had 11 LOSR and 9 CC events (Figure 6.15). The other two patients who had surgery (SL, MR) had borderline measurements for oesophageal acid exposure and symptom association (TR 4.5% and SI for HB 50% for patient SL; TR 5.4% with negative SI for patient MR) although both had HRM findings that were suggestive of GORD: hypotensive dysmotility and increased frequency of post-prandial LOSR events (6 and 7 events respectively).

3 patients (CG, DO, AA) had similar HRM findings as above (hypo-/aperistalsis with frequent post-meal LOSRs). All had clear pathology on pH-studies (TR 15%, 16% and 38% respectively with SI >50% for all) which corroborated the manometry findings. All three were offered anti-reflux surgery; however 2 declined (CG, DO) and 1 was not fit for an operation (AA; Figure 6.11). CG and AA have ongoing symptoms which are refractory to maximal therapy, while DO has responded well to twice daily Nexium. The remaining 3 GORD patients (JB, MO and JJ) were not offered anti-reflux surgery; JB had symptomatic oesophageal spasm (100% D-SI for dysphagia; Figure 6.10) and MO had OGJ outflow obstruction detected only during the meal (100% D-SI for chest pain). Both JB and MO have persistent symptoms. JJ had severe hypotensive dysmotility during all modalities and this was likely related to connective tissue disease. His ambulatory pH

study was only mildly elevated (TR 5.8%) with negative symptom association; however JJ described good symptom control with optimised Ranitidine and Domperidone.

Functional Heartburn patients

Of the 7 FH patients, none underwent anti-reflux surgery. DP and SM had normal manometry findings with no symptoms and a normal post-meal LOSR frequency. Such results suggest a true positive FH diagnosis. Symptoms resolved with dietary intervention and stress reduction respectively and no medication was required.

Two patients had manometric changes supporting a diagnosis of GORD despite negative ambulatory catheter-based pH monitoring: i) KS had hypotensive dysmotility with 70% D-SI for dysphagia in which 7 dysphagia episodes coincided with hypo-/aperistalsis and 5 LOSR events occurred during the observation period. ii) RB (Figure 6.9) had an unstable LOS noted during bread swallows and test meal with 100% D-SI for dysphagia and 4 LOSR events during the post-prandial observation period. Symptoms resolved in both with optimized acid-suppressant therapy, and in KS symptoms recurred on stopping medication. Therefore this was suggestive of a false-negative initial 24 hour pH result and it was recommended to the referrer that these patients might benefit from prolonged wireless pH monitoring if symptoms become refractory to acid-reducing medications, especially if anti-reflux surgery was being considered (Chapter 4).

CC, IS and JW had symptomatic oesophageal dysfunction during the test meal. None had evidence of GORD on pH testing and symptoms failed to resolve with optimised acid-suppressant therapy. CC (Figure 6.13) and IS (Figure 6.15) had OGJ outflow obstruction only during free drinking and the test meal (100% D-SI for dysphagia) but not with water or bread. Both were referred for dilation. CC described resolution of symptoms after OGJ dilation; although the procedure had to be repeated twice within the 2 year follow-up period. IS, who is elderly and frail was still awaiting the procedure and remained symptomatic at 2 years. JW (Figure 6.14) had achalasia after free drinking and meal studies (100% D-SI for dysphagia); however likely in view of her age and frailty, the referring physician was reluctant to offer surgery. She was informed that she may receive dilatation or botox if symptoms persisted.

GORD					
patient	**5ml water**	**1cc bread**	**meal**	**Post meal/MWS**	**Outcome**
AA	normal/nondiagnostic	normal/nondiagnostic	*hypo/aperistalsis*	*Post meal - Frequent LOSR*	Surgery not offerred due to aperistalsis Excellent response to PPI
JB	resistance to flow at LOS	resistance to flow at LOS	*oesophageal spasm*	*MWS - No LOS suppression*	DOS/resistance to flow not addressed No response to PPI
CG	normal/nondiagnostic	normal/nondiagnostic	*hypo/aperistalsis*		Declined surgery No response to PPI
RH	hypo/aperistalsis	hypo/aperistalsis	*oesophageal spasm*		Excellent response to surgery
JL	hypo/aperistalsis	hypo/aperistalsis	*normal/nondiagnostic*		Excellent response to surgery
SL	hypo/aperistalsis	*normal/nondiagnostic*	*normal/nondiagnostic*	*Post meal - Frequent LOSR*	Excellent response to surgery
MO	normal/nondiagnostic	normal/nondiagnostic	*resistance to flow at LOS*		Stricture not addressed Poor response to PPI
MR	hypo/aperistalsis	*oesophageal spasm*	*oesophageal spasm*	*Post meal - Frequent LOSR*	Excellent response to surgery
Functional heartburn					
patient	**5ml water**	**1cc bread**	**meal**	**Post meal/MWS**	**Outcome**
RB	normal/nondiagnostic	*unstable LOS*	*unstable LOS*	*MWS - DOS following drink*	Excellent response to PPI
CC	hypo/aperistalsis	*resistance to flow at LOS*	*resistance to flow at LOS*	*MWS - No LOS suppression*	Excellent post dilatation
IS	normal/nondiagnostic	normal/nondiagnostic	*resistance to flow at LOS*	*MWS - No LOS suppression*	No therapy - symptomatic until lost to F/U
JW	hypo/aperistalsis	hypo/aperistalsis	*resistance to flow at LOS*	*MWS - No LOS suppression*	Awaiting Botox Still symptomatic

Table 6.23 Outcome following physiological challenge swallows.

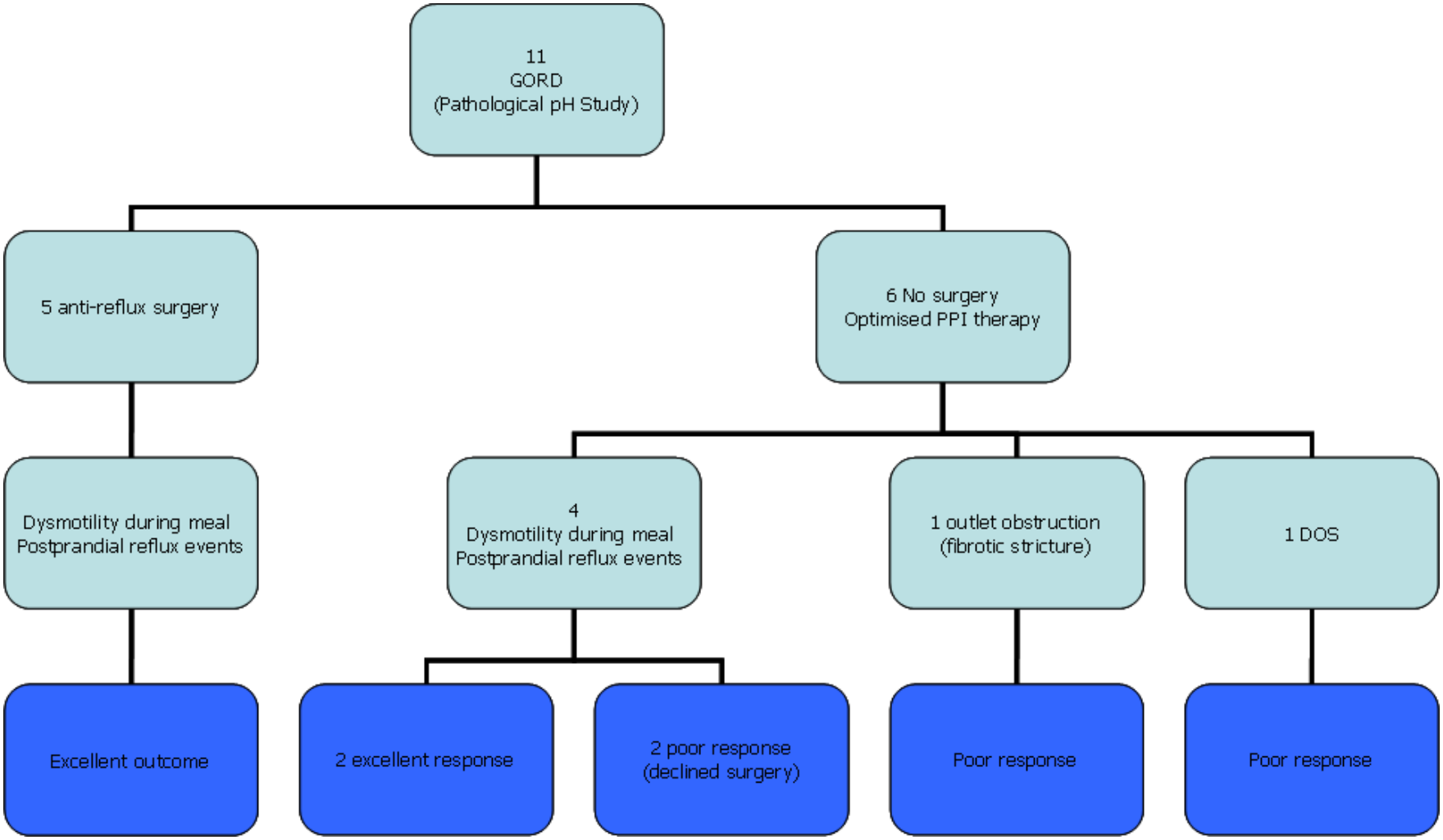


Figure 6.17 GORD 2 year outcome algorithm

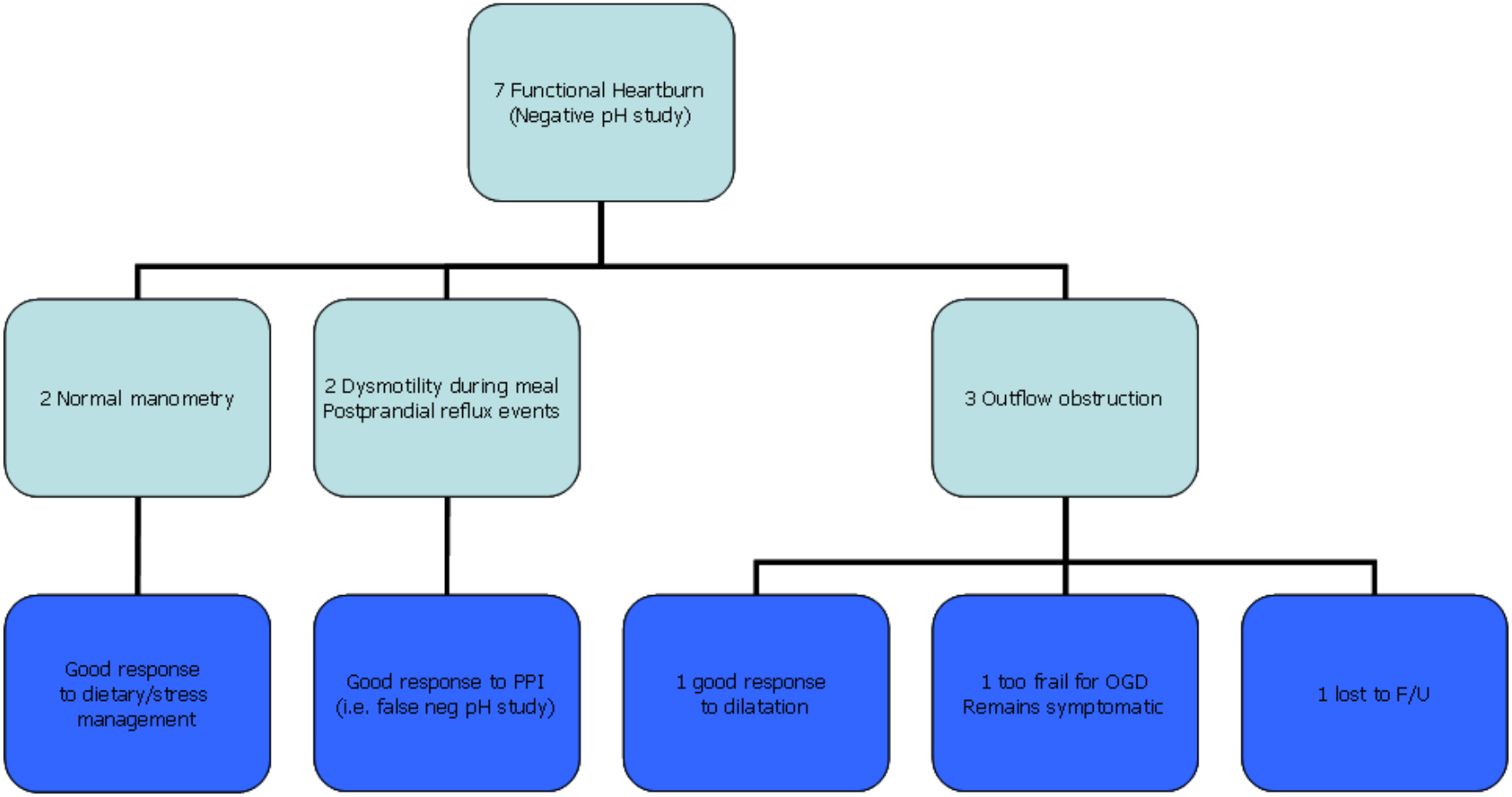


Figure 6.18 Functional Heartburn 2 year outcome algorithm

6.4 Summary of results

- High Resolution Manometry facilitates the assessment of oesophageal function and the detection of symptomatic dysfunction during normal eating and drinking.
- A methodology for the detection and analysis of oesophageal dysmotility during and after a standardised test meal and free drinking was introduced.
- A novel metric which measures the association of symptoms with dysmotility was presented.
- Reproducing normal swallowing behaviour in the 'physiological' upright-seated position had important effects on oesophageal physiology which induced dysmotility and typical symptoms.
- Meal consumption was associated with more ineffective swallows in patients compared to healthy subjects (28% vs. 51%; $p<0.001$)
- An effective post-MWS oesophageal contraction was seen in 80% of healthy subjects and 39% of patients ($p=0.055$).
- Patients reported symptoms during solid swallows (single swallows and the test meal), free drinking and the postprandial observation period that were not present with single water swallows. No symptoms occurred with single water swallows although 9/12 (75%) patients with symptom associated dysmotility had a positive dysmotility symptom index during the test meal or postprandial observation.
- Associating symptoms with dysmotility increased the sensitivity for detecting oesophageal motor disorders, improved diagnostic yield and influenced outcome. Compared to single water swallows alone, 12/18 (67%) patients had a change in manometry diagnosis during the test meal.
- 2 year follow-up studies suggest that normal eating and drinking during HRM testing may help guide management.

6.5 Discussion

This study proposes a paradigm shift in the assessment of oesophageal function by expanding the utility of existing High Resolution Manometry technology. Most importantly it provides evidence of how the classification of oesophageal dysmotility based on the identification of *symptomatic* oesophageal dysfunction while drinking and eating freely were superior to the current standard of detecting (any) dysmotility during single supine water swallows in reaching a clinically relevant diagnosis and influencing outcome.

In the literature and in clinical practice, there is a poor understanding of how oesophageal dysmotility causes symptoms and many patients that undergo conventional manometry receive no clear diagnosis because results produced are not necessarily geared towards identifying symptoms.[15,16] As seen in Chapter 5, even in health, many swallows can be considered to be abnormal, and without correlating these with symptoms there is an increased likelihood of providing a false positive diagnosis in a well individual. Combining conventional manometry with imaging or impedance can improve diagnosis and stratify patients in terms of oesophageal (dys)function;[46,293] however the mechanisms of dysfunction and disease still lack clarity. HRM with closely spaced (21-36) sensors extending from the pharynx to the stomach clarifies the relationship between contractile force (motility) and the forces that drive bolus transport and reflux (function).[243,291,292,294] Still, even with HRM, studies that focus on single supine water swallows only provide an indirect assessment of the causes of symptoms that might occur during or after normal eating behaviour, with no real emphasis on reproducing relevant symptoms. Although it is the current standard, this may be inaccurate with far-reaching consequences not only on diagnosis but also on treatment decisions. The new emphasis on symptoms presented here is analogous to the shift in ambulatory reflux studies away from GORD diagnosis based only on oesophageal acid exposure to the modern definition of GORD which also includes the association of reflux events with symptoms.[1]

Studies in this chapter showed how HRM can facilitate the analysis of relatively complex pressure data during drinking and eating. New techniques were standardised and novel

metrics were formulated which included symptom association in the final assessment. These techniques were then used to clarify the association between oesophageal dysmotility, dysfunction and symptoms which could influence therapy and outcome at two years. Furthermore, a postprandial observation period following a refluxogenic meal also provided insight into the mechanisms by which reflux events and their associated symptoms occur.

The results confirm that by increasing the workload on the oesophagus and by reproducing normal eating and drinking behaviour, symptoms can be reproduced and the dysmotility that is related to these symptoms can be identified. Spontaneous reports of oesophageal symptoms were rare during water swallows, even in the presence of oesophageal dysmotility, but common during the test meal. In contrast, healthy volunteers (Chapter 5) were able to complete the meal and post-prandial observation period without complaint.

Failed swallows and hypotensive dysmotility with water swallows were more common in patients compared to healthy controls. As reported previously,[245] in several patients with endoscopy negative GORD, oesophageal motility 'normalised' with solid swallows resulting in improved peristalsis coordination and increased contractile pressures (Table 6.7 and patient JL Figure 6.12).

A variety of 'dysmotility events' were observed during the test meal. Although such events also occurred in healthy subjects (Figure 6.6a), the functional significance of the higher rate of abnormal swallows in the disease group is supported by the finding that patients took almost 30% longer than controls to complete the meal (median 399 vs. 552s). This implies that patients with oesophageal disease try to compensate for underlying dysmotility and dysfunction by eating more slowly and producing an increased number of swallows even if these 'events' do not produce overt symptoms. In general, 12/18 (67%) patients had a change in diagnosis based on extending the HRM studies beyond water swallows.

Detailed analysis revealed that various abnormal pressure events were associated with symptoms during the test meal (Table 6.9 - 6.20). Some were clearly pathological and included: aperistalsis, outlet obstruction (increased intra-bolus pressure above the OGJ with or without pan-oesophageal pressurization) and high-pressure oesophageal spasm. Other events were simply more common in patients including: failed swallows, hypotensive peristalsis and low-pressure spasm. What differentiated the groups was that ineffective swallows in healthy subjects were commonly followed by an effective, primary or sometimes secondary peristalsis event, whereas patients tended to produce several abnormal swallows in sequence. Such behaviour would be expected to increase bolus retention and oesophageal wall stretch (distension) which could therefore illicit symptoms.[295,296] (Figure 6.5)

Free drinking provided further evidence of resistance to bolus flow in those with a non-relaxing LOS. This was especially true for patients with achalasia as the accumulation of water followed by typical symptoms (regurgitation/cough) could be seen (by the patient and doctor) and measured (e.g. patient JW Figure 6.14). MWS could also identify patients with outflow obstruction not always noticed with other testing modalities; of the 5 patients with increased suppression of contractility on MWS, 2 (JB and MR) comprised of patients with GORD on pH testing. This raises the suspicion of a fibrotic stricture related to chronic reflux. At two years follow-up, JB (Figure 6.10) continues to complain of symptoms of dysphagia and reflux not responding to acid reducing medication while MR had anti-reflux surgery with complete resolution of his symptoms.

An effective post-MWS oesophageal contraction was seen in 80% of healthy subjects, and 39% of patients (p=0.055). Further sub-analysis showed that compared to health an effective post-MWS oesophageal contraction was seen in just over half (57%) of those with FH (p=0.593) but was less prevalent in patients with GORD (27%; p=0.030). Daum et al[245] showed that patients with severe GORD were less likely to have effective swallows to solids compared to healthy subjects. Therefore a similar response to increased workload on the oesophagus may also be occurring here, albeit with the post-MWS clearance of accumulated water rather than single bolus solid swallows.

After the test meal, transient (TLOSR) and swallow associated lower oesophageal sphincter relaxations (SLOSRs) were observed in both healthy subjects and patients (Figure 5.15 and 6.15). Many of these were accompanied by common cavity events (i.e. reflux); however, without pH and impedance, it is not clear whether such reflux events were acid/non-acid, liquid or gas. Consistent with previous reports,[297] the overall frequency of these LOS relaxations was similar in patients and controls (Table 6.21 and Chapter 5 Table 5.10); however, on closer scrutiny an increased frequency of reflux events (especially SLOSRs) was noted in many individuals with GORD and, crucially, 'reflux symptoms' related to these events were only reported in patients. This may be associated with the volume and composition of the refluxate in these patients, or an increased sensitivity to normal reflux.[2,151] Additionally, HRM detected behavioural abnormalities such as rumination in some patients that would require biofeedback rather than medical management.[298]

It is clear that many 'dysmotility' and 'reflux events in patients did not produce symptoms and, conversely, symptoms were not always preceded with dysmotility. This inconsistent association between physiological events and symptoms is typical in functional gastrointestinal diseases and has been extensively studied in GORD.[76] In this study, techniques used in ambulatory pH monitoring were adapted to provide a quantitative assessment of symptom association with dysmotility during and after the meal. This was a novel approach not yet considered in the literature. Symptoms associated with dysmotility (SAD) were defined as abnormal pressure events or reflux that preceded reports of symptoms within a 10 second interval. This short time window maximized the likelihood of causal association. The oesophageal dysmotility Symptom Index (D-SI) was then defined as the percentage of SAD divided by the total number of symptoms reported by the patient.

Applying Symptom Association Probability (SAP) to determine the probability that dysmotility events were followed by symptoms was considered;[76] however there were limitations to this approach. First, SAP gives a measure of 'statistical confidence' but no indication of 'effect size' and is unreliable if the number of 'events' is small. In contrast D-SI is sensitive to symptoms that are related to intermittent oesophageal dysfunction.

Moreover, considered together with the frequency and severity of events, D-SI provides an indication of patient responsiveness to oesophageal dysfunction (i.e. visceral sensitivity and/or vigilance).[151] In other words, one D-SI could be compared to another and the closer the D-SI approaches 100% the more likely the association of reflux with symptoms is real. Looking ahead a method that combines the practical advantages of SI with a better assessment of statistical confidence is required, and in fact this is being developed for ambulatory pH studies at St Thomas' Hospital.[299]

In the absence of a 'gold standard' test, outcome data provides insight into the clinical impact of diagnostic tests. Although the patient group studied was small and heterogeneous, these findings provide initial evidence that methodology which includes a test meal, free drinking and post-prandial observation can provide useful and effective information. Patients with frequent symptomatic reflux events after the meal had excellent functional outcome after anti-reflux surgery even if ambulatory pH studies were borderline. Similarly, two FH patients who had similar HRM findings to the GORD group had a good response to optimized acid-suppression. Thus HRM appeared to be complementary to reflux studies in those with clear pH pathology, and was also able to detect GORD in those with no definitive results on ambulatory pH studies. Additionally, this approach identified oesophageal dysmotility and dysfunction that had not been detected with other forms of testing, including endoscopy and HRM with single water swallows. These findings included individuals with significant outflow obstruction due to structural or functional pathology. Thus, observations during and after a test meal did not only provide insight into the mechanisms of disease but also guided clinical management, including in patients with otherwise unexplained symptoms.

6.6 Conclusion

In conclusion, this study showed that the inclusion of single solid swallows, a test meal, free drinking and a post-prandial observation period into routine HRM testing provided clinically relevant information that could explain the pathological basis of symptoms and establish a relevant diagnosis in patients presenting for investigation of ‘oesophageal symptoms’. A standardised methodology for HRM investigation and analysis of oesophageal dysmotility and symptoms during and after eating and drinking was presented. Classification of pathology was based on normative values achieved from healthy subjects. The long-term clinical outcome of this patient group indicated that these observations do not only increase diagnostic certainty and yield, but also guide effective clinical management. Larger studies are now in progress to confirm the clinical utility and cost-efficiency of this approach.

Chapter 7

Summary and Future direction

7.1 Prolonged wireless pH monitoring (BRAVO)

Patients referred for ambulatory 24 hour catheter-based pH monitoring may not always receive a correct diagnosis**.** There are several possible explanations for this discrepancy:

1) Intolerance to insertion of the nasal catheter
2) In those who tolerate insertion, nasal and pharyngeal discomfort and social embarrassment reduce oral intake and impact on behaviour.
3) With its wide day-to-day variability, brevity of the 24 hour studies may impact on diagnostic accuracy.

Studies in this thesis demonstrate how prolonged measurement with wireless pH monitoring can address these concerns. Chapters 3 and 4 showed that 2/3 of patients who were either intolerant to the nasal catheter or had negative results yet ongoing typical symptoms were shown to have evidence of GORD with prolonged (≥48 hour) wireless pH monitoring. Improved comfort and tolerability facilitated normal dietary and physical behaviour which increased the number of naturally occurring reflux and symptom events.[81,82,84] Additionally, increasing the duration of study beyond 24 hours appeared to improve the reliability of diagnosis, especially in patients with intermittent symptoms. These results are of more than academic interest. Follow-up results from Chapter 4 (and others[106]) suggest that this technology improves the ability to predict outcome following treatment with acid suppression therapy and/or anti-reflux surgery. This technology is not widely available, and many patients who fail catheter-based testing or experience undue discomfort do not receive an accurate or definitive diagnosis. This can lead to suboptimal treatment choices.

In summary, prolonged measurement is better tolerated, improves diagnostic reproducibility and reduces measurement variation as it increases the number of 'events' available for analysis.[85,106,261,262] It is most suitable for those with wide day-to-day variability of oesophageal acid exposure[87] and in patients with intermittent symptoms

(e.g. less than 6/day) in whom it is difficult to establish a statistically significant and reliable symptom association.[85,105,106]

In all, these studies suggest that wireless pH monitoring for 48 (and up to 96) hours is superior to 24 hour catheter-based pH monitoring. On the other hand, wireless pH monitoring is expensive and, in keeping with UK national guidelines, is most commonly reserved for cases where patients are either intolerant to the catheter or have negative results despite typical symptoms of GORD. Until the evidence-base improves, Bravo will remain a second line investigation. Conversely, other emerging technologies and novel methods (High Resolution Manometry with challenge swallows; Chapter 5 and 6) might help discriminate between normal individuals and disease, and are not subject to limitations imposed by national guidelines.

7.1.1 Limitations of Bravo studies

Chapter 3 limitations

Although patients were recruited from the same referral pool, those who were in the Bravo group may have represented a different cohort of patients as a result of their intolerance to the catheter. Although it would have been interesting to include a cohort of patients in whom both the catheter and Bravo capsule were analysed simultaneously, physical interference of the catheter with the capsule risked iatrogenic early capsule detachment. Furthermore, a dual-sensor or Impedance-pH assessment to exclude proximal reflux sensitivity was not performed. On the other hand, this study represents true clinical practice with strict adherence to NICE guidance whereby patients proceeded to Bravo when catheter-based studies were unsuccessful.[102] Furthermore, had Bravo not been available, many patients would not have achieved a diagnosis of GORD; however the impact of these findings based on diagnostic outcome was not addressed and is a major weakness of this study.

Chapter 4 limitations

This highly selected group of patients was referred by physicians and surgeons due to the clinical suspicion of a 'false negative' diagnosis on an initial catheter-based pH study. Thus these findings cannot be generalized to all patients with negative C-pH, many of whom have atypical reflux symptoms that are much less likely to be caused by gastro-oesophageal reflux events.[91] Furthermore the catheter-based studies performed at St Thomas' Hospital did not routinely include impedance which is reported to increase test sensitivity 'off PPI therapy' by up to 20%.[91] Although theoretically Impedance-pH could have reduced the pool of patients entering the study, the principle limitations of 24 hour catheter-based studies still applied and it was unlikely that this technology would have removed the requirement for prolonged wireless testing in some patients.

More critically, this study did not have a control group. Inclusion of patients with a positive C-pH study would have provided information about the concordance and day-to-day consistency of GORD diagnosis between methods. In other words, the results are biased in 'favour' of prolonged wireless pH monitoring in that the diagnosis could only either remain the same or change from negative to positive for GORD and not the other way.

A true 'gold standard' does not exist. Therefore outcome data was critical. There were a high proportion of patients with a negative C-pH who then had a positive GORD diagnosis on Bravo and a good outcome following anti-reflux surgery. This provided support for the utility of this investigation. Despite these limitations, study procedures reflected 'real life' clinical practice in which most patients were re-referred for further testing only if reflux symptoms did not respond to initial therapy, patients had ongoing typical symptoms and the referrer wished to confirm the diagnosis prior to proceeding to surgery.

Bravo; areas of interest

Results from Chapters 3 and 4 were presented using different formats, durations and cut-off values as the most appropriate analysis method for this novel technology is yet to be established. As with any technological advance several areas of contention remain:

- What is the optimal duration of Bravo?
    - 48, 72, 96 hours, longer?
- What is the most appropriate analysis method?
    - Worst day or Average?
- What cut-off values should be used for the various parameters?
    - Total reflux = 4.2%[250], 5.3%[103] or 5.78%[258] ?
    - Should different cut-off values be also established for Upright and Supine reflux?
- What is the most appropriate pH threshold?
    - A fall in pH below 4, 4.5 or 5 threshold or a >1pH or 2pH unit drop?
- What is the most appropriate reflux-symptom association method?
    - Symptom Index (SI; measures effect size, not confidence)
    - Symptom Association Probability (SAP; measure of confidence, not size)
- What event → symptom time window provides the most sensitive and specific reflux-symptom association measurement?
    - 1 min, 2 min or other?

As described in Chapters 3 and 4, the optimal duration of study and the most appropriate analysis method for oesophageal acid exposure and reflux-symptom association analysis have not yet been determined. Studies show that prolonged monitoring improves the diagnostic yield; however outcome is also dependent on the analysis methodology. In general, results based on 'Average cumulative' measurements are statistically robust and stable over time with high specificity for GORD diagnosis.[85] With 'Worst day' analysis, a steady increase in yield is observed (Chapter 3 and 4). This is the result of high day-to-day variation in oesophageal acid exposure such that prolonging monitoring increases the number of patients considered to have GORD over time if this decision is based on any given 24 hour period exceeding the diagnostic threshold. While 'Worst day' analysis

might be appropriate in patients with intermittent symptoms, specificity decreases and the risk of a false positive diagnosis increases.[85,266] Nevertheless, 'Worst day' analysis is the most widely presented in the literature,[85,103] and is commonly used at the St Thomas' Hospital Oesophageal Unit and other major centres. As the aim of studies in this thesis was not to identify which analysis method was more statistically appropriate or clinically relevant, both 'Worst day' and 'Average' analyses were presented throughout.

Notwithstanding the possible advantage of prolonged studies, there must be a limit to the 'Worst day' approach. For example, it would be wrong to select 1 abnormal day out of 20 days monitoring as it would be expected that even healthy subjects are likely to be labelled as having GORD by chance alone. One simple approach that can be applied in clinical practice is to decide at 48 hours whether to prolong the Bravo study; if the first 2 days provide consistent results (i.e. both clearly positive or negative) then it is unlikely that the subsequent 2 days will alter the diagnosis and further prolongation is likely to be unnecessary. Conversely, if the results of the first 2 days are inconsistent, borderline or widely variable, prolonging the study duration would provide more data on which to base a definitive diagnosis. Alternatively, in patients with borderline or inconsistent results within the first two days of Bravo, High Resolution Manometry with challenge swallows and post-prandial observation (described in Chapter 6) might help bridge the gap of uncertainty; a future study worthy of consideration, although the challenge of catheter intolerance remains.

Another question that needs to be addressed in future studies is in regards to parameters that measure reflux-symptom association. Only Symptom Index (SI) was available at St Thomas' Hospital Oesophageal Lab during the initial Bravo studies (Chapter 3), subsequently SAP was included in Chapter 4. In the literature, both are intermittently used in isolation or in combination; however it remains unclear which provides the best and most clinically relevant summary. Neither SI nor SAP provides an ideal assessment of reflux-symptom association. SI does not take into account that the association between reflux and symptoms may occur by chance. In other words, if only one symptom event occurs and this happens to be associated with a reflux event by chance, this still produces an SI of 100%. Therefore if the number of reflux and symptom events are not included,

results need to be considered with caution.[76] On the other hand SAP lacks the specificity required for prolonged studies as it is not stable over time (i.e. the chance of a positive SAP increases with study duration independent of disease severity). For the same reason, SAP cannot be used to compare the severity of disease between patients.[76,151,300] Indeed in Chapter 3, agreements between diagnoses based on SI and SAP were far from perfect. Presently, in routine clinical practice at St Thomas' Hospital, both parameters are presented to the referrer and the study is considered positive if either measurement is positive. Although studies in this thesis were not designed to address this question, the large dataset from prolonged monitoring greatly facilitate a statistically robust assessment of reflux-symptom association.[151,300]

7.2 High Resolution Manometry with physiological 'challenge swallows'

The purpose of the oesophagus is to move food and fluid from the pharynx to the stomach and to minimise gastro-oesophageal reflux. Coordinated peristaltic activity is a multi-step process which usually requires:

(i) a pharyngeal swallow that "pumps" food and fluid into the oesophagus

(ii) gravity (weight of swallowed food and fluid)

(iii) effective oesophageal motor function (deglutative inhibition followed by peristaltic contraction)

(iv) sufficient relaxation *and* opening of the oesophago-gastric junction

(v) a positive intra-bolus pressure gradient (i.e. a pressure drop from proximal to distal).

In a healthy subject, all the above steps are usually satisfied. In disease, small volume water swallows can mask pathology as it can usually be cleared with an intact pharyngeal pump and passive gravitational drainage alone as long as the lower oesophageal sphincter (LOS) and oesophago-gastric junction (OGJ) relax (i.e. no achalasia) and open (i.e. no outflow obstruction). Indeed this passive clearing mechanism is observed in patients with hypo-/aperistalsis (e.g. severe GORD or connective tissue disorders such as scleroderma).

To better define pathology, an understanding of structure and function is required that extends beyond point measurements of contractility of conventional manometry, and defines parameters that are key to effective bolus transport.

The Chicago Classification[125,131,247] has been imperative in improving the understanding and categorising oesophageal and oesophago-gastric junction dysmotility, an important hurdle when considering therapeutic options. For example it has described three achalasia subtypes based on their (high resolution) manometric signature and therapeutic response.[136,301] Although less definitive, the Chicago Classification has also helped re-define other phenotypes of dysmotility (e.g. hypotensive [294] and hypertensive[302] oesophageal dysmotility) that might respond to therapy.[36,303] Nevertheless, standard methodology using HRM fails to establish a definitive diagnosis that can explain the aetiology of symptoms in many patients presenting with dysphagia or reflux.[111,126] This is likely because tests based on small volume water swallows do not 'challenge' the oesophagus sufficiently nor do they represent normal behaviour, therefore symptoms are rarely triggered. Chapters 5 and 6 described novel methodologies which expand the utility of HRM by increasing consistency/volume of bolus (single bread swallows, eating and free drinking) while in the physiological upright, seated position. This and the addition of a 10 minute post-prandial observation period provided a better understanding of oesophageal (dys)function in health and disease. Furthermore, the emphasis shifted away from only assessing aberrant motility, and included interpretation of its association with symptoms. This is because in real life symptoms take place almost exclusively during and/or shortly after meals. Such observations could explain the cause of symptoms and may have the potential to direct specific medical, behavioural or surgical therapy, as well as identify patients who are inherently normal. (Chapter 6)

Although intuitively obvious, these techniques have not entered routine clinical practice. This is likely because of the difficulty in interpreting the complex HRM findings and the absence of a standardised methodology with normative values. Chapters 5 and 6 developed and applied new techniques by which HRM could be used to facilitate the assessment of complex pressure activity while eating and drinking. Furthermore, reference values were formulated and used in the assessment of patients. These studies

showed that in both healthy subjects and patients, the oesophagus responded to solid swallows by improving coordination and increasing contractile vigour of peristaltic contraction.[276] Using these techniques, challenge swallows identified pathology not detected with standard water swallows. Moreover, as these techniques reproduced normal behaviour, typical relevant symptoms were triggered and the frequency by which these coincided with dysmotility was measured using a parameter akin to the symptom-association of reflux studies. In Chapter 6, when all study conditions were taken into account (single water and bread swallows, free drinking, test meal and post-prandial observations), 67% patients showed a change in diagnosis compared to water swallows alone.

7.2.1 Limitation of HRM studies

Chapter 5 limitations

1) This study might be criticised because normative values for each study condition (change in position and bolus consistency) were based on five swallows in each position rather than the traditional 10 (water) swallows which constitute reference values in the literature.[125,247] In addition, the numbers of patients used in the analysis (especially during the standardised meal, MWS and postprandial observation) were small and this needs to be taken into account when formulating normative data. Finally, it is not clear if the lack of correlation between the number of effective swallows and the time it took to complete the meal was due to a type I error as only 10 healthy subjects were included in the study. However, with the inclusion of bread swallows and a test meal, the overall number of swallows available for analysis was many times greater. Moreover as normal, physiological, eating behaviour was reproduced, this provided additional and more detailed information regarding the swallow mechanism that single water and bread swallows did not and, as will be shown in Chapter 6, produced a diagnostic yield that was superior.

2) Investigators that performed the data analysis were not blind to the study conditions (i.e. position change, bolus consistency); however for inter-observer agreement analysis was performed by independent physicians in different countries without the benefit of any subject information (e.g. age, sex, name). Furthermore, for healthy volunteer (and

patient) analysis, the standardised meal, MWS and post-meal observation studies were all performed in the upright position and were technique specific which precluded the necessity for blinding in regards to position change or bolus consistency. Finally, all volunteer (and patient) analysis was carried out from the original HRM trace one year after being collected while blind to subject demographics and presenting complaint.

3) Previous studies presenting normal values for HRM-based water swallows selected only single pharyngeal deglutitions that were followed by effective peristaltic contractions for analysis (i.e. multiple deglutitions and also failed contractions were not included);[125,247] however for solid swallows it is not uncommon for more than one pharyngeal deglutition to be required before a bolus is successfully transported.[304] Therefore to analyse only successful swallows is not representative of normal physiology, and in this study a range of 1-3 deglutitions were sometimes required for the successful transport of solid bolus swallows. The frequency of pharyngeal swallows that preceded peristalsis was related to individual behaviour in response to increased bolus consistency as well as catheter-related pharyngeal irritation. Nonetheless, when key parameters which describe oesophageal function were compared, no differences were found between single and multiple pharyngeal swallows.

Chapter 6 limitations

Normative values were based on the results of only 10 healthy controls and patient data was acquired from 18 patients with both reflux and dysphagia symptoms; however, this relatively small number of participants was offset by the amount of data available for analysis (240 minutes eating and 280 minutes postprandial observation time). Larger studies would provide more robust information about the prevalence of asymptomatic non-pathological dysmotility in healthy subjects and also the number of ineffective swallows in sequence that occur before symptoms are likely to be reported. Nonetheless the current findings suggest that the presence, not only of symptoms, but of *symptomatic dysmotility* during and after bread swallows/meal/drink thoroughly discriminates between patient and healthy subjects.

Although longer prandial and post-prandial observation periods and/or ambulatory studies would provide more information, such brief observations are informative because (i) dysmotility during meals is related to swallowing problems which reproduce relevant symptoms and (ii) sphincter relaxations and reflux events are most common immediately after meals.[305] Such a brief study can be reproduced in routine clinical practice and provides important and discriminating information which can influence outcome.

Another limitation was that the same clinician that recruited patients and performed the tests also performed the data analysis. To minimise bias due to lack of blinding, a clear, *a priori* definition of oesophageal dysmotility was applied based on studies presented in Chapter 5 that demonstrated high inter-observer reproducibility.[275] Additionally, only spontaneous reports of symptoms were recorded and a very narrow time window (10 seconds) was utilized to define the association between dysmotility and symptoms.

HRM; areas of interest

A recent study showed that although hypotensive dysmotility with water swallows is common in endoscopy negative reflux disease, only failure to respond to the 'challenge' of bread swallows was associated with poor bolus clearance and increased oesophageal acid exposure (pH-monitoring and endoscopy).[245] This new observation shows how oesophageal function can be affected even in chronic reflux disease. (Figure 7.1).[271,290]

Techniques described in Chapters 5 and 6 have also helped identify non-benign pathology missed during other investigation pathways. The case presented in Figure 7.2 is an example of a patient who's presenting symptoms, endoscopic findings and HRM with water swallows were unremarkable. If it was not for 'challenge swallows' the underlying OGJ malignancy would not have been suspected and investigated further.

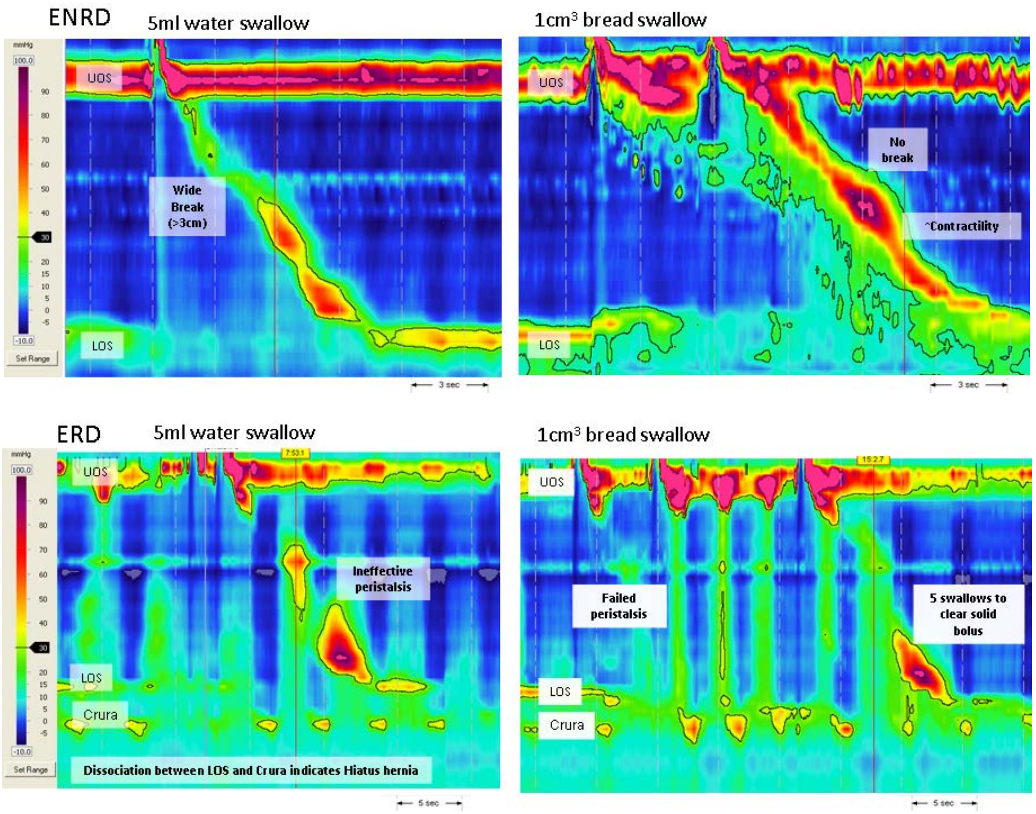


Figure 7.1 HRM of ENRD and ERD. Water and solid swallows of 2 patients with endoscopy negative reflux disease (ENRD; top panels) and erosive reflux disease (ERD; bottom panels).

Left top and bottom panels: Water swallows show ineffective peristalsis with a wide (>3 cm) separation between the proximal and mid-oesophageal contractions

Top right panel: In contrast, solid swallows show an 'effective peristaltic response' only in the patient with ENRD. Bottom right panel: Solid swallows produce a failed peristalsis in the patient with ERD.

Note: a small hiatus hernia is seen in the patient with ERD (bottom)

(Reproduced from Daum et al Neurogastroenterol Motil 2011[245])

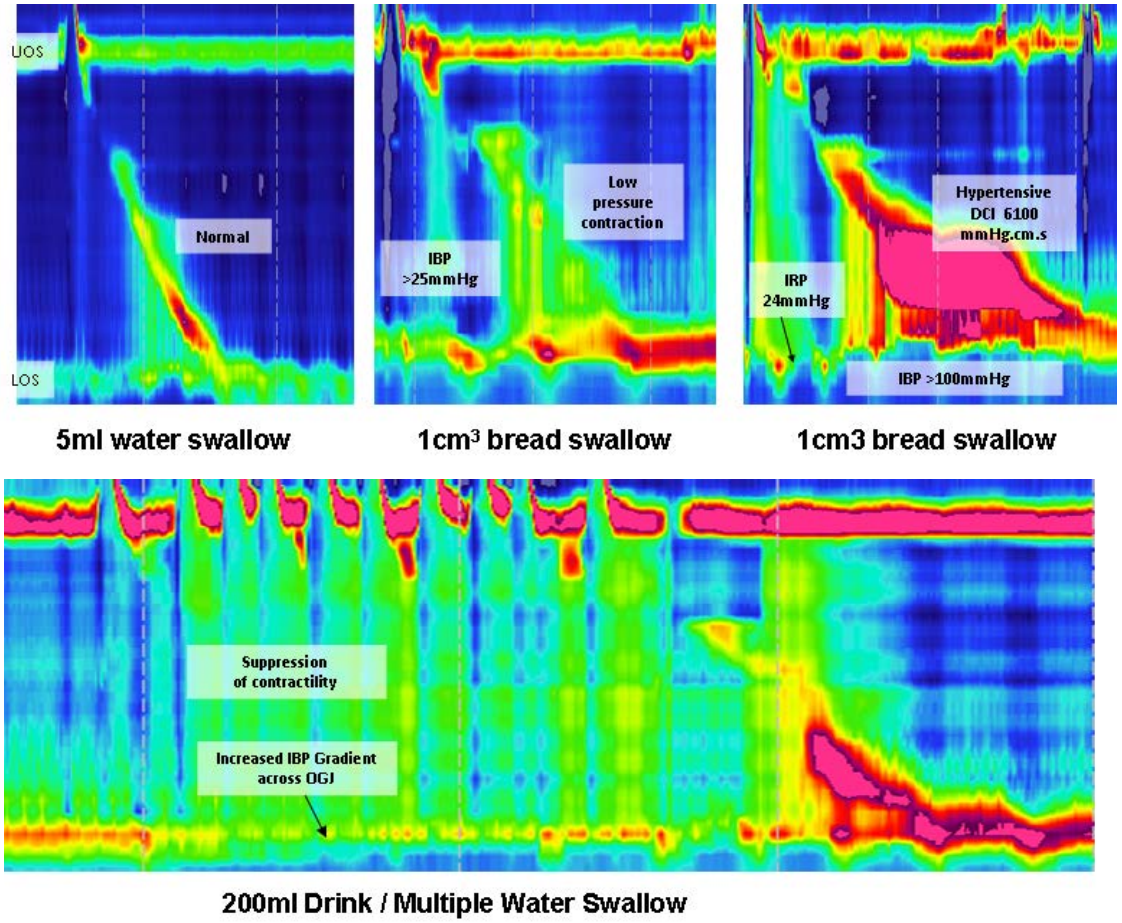


Figure 7.2 HRM of patient with a submucosal tumour at the OGJ. 41 year old gentleman who presented with minimal symptoms of food and fluid regurgitation and some mild dysphagia to solids. Endoscopy was normal.

Top left panel: 5ml water swallows showed hypotensive dysmotility with only a marginally wide (3 cm) proximal transition zone, a feature not uncommonly found with small volume water swallows in the upright position.

Top middle and right panels: Solid swallows showed a raised IRP of 24.3 mmHg with variable ineffective peristaltic response (segmental spasm (middle panel) and nutcracker oesophagus with a peak DCI 6100 mmHg (right panel)) as well as evidence of obstruction at the level of the lower oesophageal sphincter (LOS) throughout. Typical symptoms of dysphagia were reproduced only with solids.

Bottom panel: Free drinking showed resistance to flow at the LOS as it did not relax.

These studies were suggestive of an obstructive pathology. Endoscopic ultrasound revealed a sub-mucosal tumour at the level of the OGJ. This patient was alive and well 1 year following chemotherapy, trans-hiatal oesophagectomy and gastrectomy.

7.3 The future

Prolonged (up to 96 hour) wireless pH monitoring and High Resolution Manometry with 'challenge swallows' provide a better assessment of patients with borderline or inconclusive results compared to the current standard. Studies presented in this thesis have standardised novel methodology and produced normative values thereby permitting these techniques to be performed routinely in any clinical practice.

Studies at St Thomas' Hospital are currently being undertaken with colleagues at the NIHR Biomedical Research Unit in Nottingham and Menne Biomed in Tuebingen Germany to address several of the areas of contention described in Section 7.1 with the aim of optimising the use of prolonged, wireless pH studies.[261] This will include outcome measurements and will be the largest set of pH data ever subjected to systematic analysis of reflux-symptom association. Prospective studies are also underway at St Thomas' Hospital and NIHR Biomedical Research Unit to investigate the impact of using the standardised meal and free drinking in a large group of patients with predominant symptoms of dysphagia.[290] The anticipated favourable outcomes may pave the way towards abandoning the 'non-physiological' single bolus test altogether.

It would be interesting to compare results of HRM with 'challenge swallows' with prolonged wireless pH monitoring in patients presenting with reflux symptoms. Furthermore, the methodology described in this thesis paves the way for ambulatory HRM, thereby assessing swallows and symptoms in a 'real life' setting *outside* of the hospital. Technological advances have already combined non-ambulatory HRM with Impedance. In the future both technologies could be combined to include ambulatory HRM with the addition of Impedance and a pH sensor yet without a nasal catheter. Such a technological advance might be achieved by temporarily securing a mid- or proximal oesophageal catheter to the oesophageal body in a manner similar to the Bravo capsule; however this too would require tolerability testing.

The ongoing progress in our understanding of oesophageal physiology and the continuous development of new technology highlights the dynamic and complex structure and function of the oesophagus and OGJ and the need for further research.

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Appendix

Appendix 1 - Information for patients attending oesophageal tests -Manometry and pH study

The aim of this information sheet is to help answer some of the questions you may have about having a manometry and 24 hour pH study. It explains the benefits and risks of the procedure as well as what you can expect when you come to hospital. If you have any questions or concerns, please do not hesitate to speak to a Clinical Physiologist for more information, the contact number is at the end of this leaflet.

What is a manometry and 24 hour pH study and why do I need these tests?

Manometry is a procedure to assess the function of your gullet (oesophagus), which may be causing the trouble you have been having recently. The test involves passing a small pressure catheter, consisting of 36 pressure sensors at 1 cm intervals, into your gullet via your nose to monitor your gullet function. The test measures the pressures and co-ordination of pressure activity within your gullet when you swallow. From this we can make an assessment of how the gullet is working and determine if your symptoms are due to certain disorders of the gullet. The test is also required before anti-reflux surgery to make sure the gullet is working well enough for you to have the operation.

The 24-hour pH study is a procedure to detect the presence of acid in your gullet. The test measures the amount of acid that refluxes (flows back) from your stomach into your gullet and will help to find out if your symptoms are caused by acid reflux.

How can I prepare for a manometry test?

Please have nothing to eat or drink for four hours prior to these tests. Water is allowed.

<u>If you are having problems fasting for four hours because you are diabetic please</u> contact us on the telephone number shown at the end of this leaflet.

Please bring with you a list of all the medicines that you are currently taking, including anything bought over the counter, or any herbal or homeopathic medicines. If you are

asthmatic, it would be helpful if you could bring your inhaler(s) with you. If you are on any blood thinning medicine (e.g. Warfarin) please inform us.

If you have been referred because of difficulty in swallowing or have the sensation of food sticking, please bring a sandwich with you which you can eat during the test. We advise female patients not to apply eye make-up for this particular test as it may cause a slight watering of the eye while inserting the tube.

What are the risks?

There is a minor risk of having a slight nose bleed or a sore throat with this procedure.

How can I prepare for a 24 hour pH study?

We ask that you temporarily stop taking any medicines for heartburn, acid regurgitation, nausea or tummy pain before the test, as they may affect the results. If your symptoms are so severe that you can't stop the medication please contact us on the number at the end of the leaflet.

Below is a list of the medication that you should stop taking, and for how long:

- **Stop taking the following tablets for seven days before the test: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole**.
- **Stop taking the following tablets for two days before the test:**

ranitidine, cimetidine, famotidine, nizatidine, metoclopramide, domperidone or cisapride.

- **Stop taking any antacids for 24 hours before the test. For example, Gaviscon®, Sucralfate, Milk of Magnesia.**

You can restart taking any of the above medicines on completion of the test.

<u>Please continue taking your other regular medicines unless you are told otherwise.</u>

Patients should wear a loose top. This is because you will be going home with the acidmeasuring tube inserted into your nose and taped over your ear, down the side of your neck, under your top and connected to the acid-monitoring recorder which is strapped around your waist. The purpose of doing this is to ensure that you can change into more

comfortable clothing later. If there is any feeling of embarrassment a scarf would help to disguise the inserted tube.

What happens during a manometry test?

You will be made comfortable on the couch, sitting upright. Local anaesthesia spray or gel is used to numb your nose. A catheter (tube) with pressure sensors along its length will then be passed through your nose and into your gullet. You should feel only a slight discomfort from this so you will not be put to sleep or sedated.

Once the pressure catheter is inserted you are allowed to rest for few minutes. You will be aware of the catheter in the back of your throat throughout the test. Although you may find it uncomfortable it will not cause you any pain.

The catheter is connected to a computer which displays and records the pressures in each sensor. During the test period we ask you to sit as quietly as possible and to talk as little as possible, and try to get used to not swallowing so frequently. This is because talking or frequent swallowing can interfere with the measurements. At some point we will ask you to take a deep breath in and out quickly to determine the position of your diaphragm. A short sharp breath is all that is required; we do not want you to hold your breath.

An exact amount of water is given through a syringe 5mls at a time (1 teaspoonful). We would like you to swallow the water in one go so that we can monitor the muscle contractions in the gullet correctly. Up to twenty swallows may be needed so that we can get an accurate assessment of the muscle activity. Please swallow normally and try not to swallow between the samples of water. We appreciate that this may be difficult but frequent dry swallow (swallowing saliva) will prolong the test.

Depending on your symptoms and our findings with the wet swallows we may also ask you to swallow several small pieces of bread or a large volume of water or milk shake. The procedure will take approximately one hour.

What happens during 24-Hour pH test?

This test will take place after the manometry in the Oesophageal Investigation Unit and will take up to 30 minutes. The testing will continue whilst you are at home over an approximately 24-hour period.

A small tube (catheter) will be passed into your gullet via your nose to monitor the amount acid reflux in your gullet. If it necessary, more local anaesthetic spray or gel are used to freeze your nose before inserting the tube. Placement of the tube in your gullet should therefore not be painful, although the back of your throat may feel slightly uncomfortable. The acid-measuring tube will be connected to a portable recorder and you will be able to return home, continuing with your normal activities.

After the tube is inserted you will be aware of the catheter in the back of your throat throughout the test but most patients find they become less aware of it with time.

This procedure requires no sedation, so you will be able to travel to and from the hospital unassisted. You may however wish to bring a relative or friend for support or company just in case the local anaesthetic affects your driving ability.

To encourage you to carry on with your normal activities in your usual environment during the test, it is important that you go home as soon as possible and do not stay in the hospital, unless there are exceptional circumstances.

Information on diet-restriction will be given to you and you will be asked to fill in a form about the times over the next 24 hours when you lie down, get up, have symptoms, have breakfast, lunch, dinner and also to state the contents of your meal.

When you come into the Oesophageal Laboratory further information will be available from us. You will need to return to the Unit on the following day at about the same time to have the tube removed. Your second appointment takes only 15 minutes. The recorder is stopped and the catheter is removed. Removing the catheter only takes two to three seconds and is not uncomfortable. The doctor will want to look at your diary sheet with you to ensure that we have all the relevant information.

Giving my consent (permission)

The staff caring for you will ask your permission to perform the procedure. It is important that you understand the benefits, risks and alternatives. If there is anything you don’t understand or you need more time to think about it, please tell the staff caring for you.

Remember, it is your decision. You can change your mind at any time. Let staff know immediately if you change your mind. Your wishes will be respected at all times. If you would like to read our consent policy, please tell a member of staff.

What do I need to do after I have gone home?

When you go home after your first appointment, if possible please follow your normal daily routine as we need to see what happens during a normal day. However, if you feel it is inappropriate to remain at work please be as active as you normally would be at home.

The recorder must not get wet so please do not have a bath, shower, or go swimming. The equipment is expensive and we ask you to treat it with care. The catheter is particularly vulnerable and if it catches on a door handle, for example, it will be irreversibly damaged and the test would need to be repeated. It is therefore advisable to wear a loose top over the recorder and catheter to protect against this.

Try to carry on with the next 24 hours as you would **normally** e.g. usual routines, normal meal times/portions, etc. But avoid acidic foods or drinks, as acidic foods and drinks interfere with the result of the test. We need to see what happens during a normal day. The catheter may move very slightly as you eat and it may feel strange but we would like you to persevere as it is important to know what happens after mealtimes.

You are requested to record when you experience your symptoms such as heartburn, regurgitation or chest pain etc. You do this:

- By pressing the marker button on the recorder every time you become aware of your symptoms (this inserts an electronic mark on to the recording), and
- By writing on the diary sheet the nature of the symptom and the time that it occurs, as displayed on the recorder
- You will also need to write down lying down and getting up times and everything you eat and drink, noting the start and finish times.

The catheter will be securely taped to your cheek and behind your ear and is not likely to move. Very rarely the catheter can be vomited back up into your mouth and in this situation you will have to remove it. To do this undo the tapes, take a deep breath in and pull the catheter out from the nose, cut the catheter off and dispose of it. Then place the recorder and your diary sheet into a box and return as arranged.

It is rare, but if you cannot tolerate the presence of the catheter you can remove it yourself as described above. Obviously if this happens we are less likely to be able to effectively diagnose and treat your problem, so please persevere with the catheter for as long as you can.

As stated above please do not take any medicines for heartburn, acid regurgitation, nausea or tummy pain during the test.

The information on the recorder is downloaded onto a computer and the results printed. The result of both the pressure recording and 24-hour pH tests will need to be carefully analysed. Your referring consultant and GP will receive a copy of the final report usually within two weeks.

Further information

Contact us

If you need further information please call the Administrative Team on 020 7188 4194 who will guide you to the correct member of staff.

Patient Advice and Liaison Service (PALS) – To make comments or raise concerns about the Trust's services, please contact PALS. Ask a member of staff to direct you to the PALS office or: **t:** 020 7188 8801 at St Thomas' **t:** 020 7188 8803 at Guy's **e:** pals@gstt.nhs.uk

Knowledge & Information Centre (KIC) – For more information about health conditions, support groups and local services, or to search the internet and send emails, please visit the KIC on the Ground Floor, North Wing, St Thomas' Hospital.
t: 020 7188 3416

Language support services – If you need an interpreter or information about your care in a different language or format, please get in touch using the following contact details.
t: 020 7188 8815 **fax:** 020 7188 5953

NHS Direct – Offers health information and advice from specially trained nurses over the phone 24 hours a day.
t: 0845 4647 **w:** www.nhsdirect.nhs.uk

Appendix 2 – Cather-based pH study instructions and diary

24 Hour Ambulatory pH Recording

Oesophageal Lab, 4th Floor Bermondsey Wing, Guy's Hospital

Date:	
Referring Dr:	
LOS Distance:	
Catheter type:	Single / Dual

Patient Details:

INSTRUCTIONS:

1) Try to carry on with the next 24 hours as you would NORMALLY. Eg Usual routines, normal meal times/portions, etc
2) Chew your food well as this will help when swallowing.
3) Record your activities on this sheet as accurately as possible.
4) Use the clock on the recorder to record the time of your activities. Press the **small oval button** to display the time. 5) Please write all times down in **24 hour clock** format.

RESTRICTIONS:

1) Avoid acidic food and drink.
   E.g PICKLES, TOMATO BASED FOODS, YOGHURT, FRUIT, SOFT DRINKS, FRUIT JUICE, ALCOHOL etc
2) Always have milk with your tea or coffee to buffer the acidity. Otherwise drink milk, hot choc, horlicks or water only.
3) Do not have a shower or bath. However you may use a cloth to wipe your self down.
4) Use a maximum of two pillows when sleeping as we need you to lie as flat as possible.

If you have any problems please ring **020 7188 4194**, Mon-Fri, 8am-4pm, excepting public holidays.

Please record any snacks, cigarettes or drinks you have. Continue over the page if needed.

START E.g. 1315	ITEM Tea and biscuit	FINISH 1330

Please record the times you are lying in a flat position.

Lying DOWN	Getting UP

Please record any exercise activities.

Start E.g. 1900	ACTIVITY Walked dog	Finish 2030

Please record your MAIN MEALS below. State the contents briefly.

BREAKFAST (today)	LUNCH (today)	DINNER (tonight)	BREAKFAST (next day)
START FINISH	START FINISH	START FINISH	START FINISH

Please record your main SYMPTOMS as it happens by pressing the ROUND button once. Only press this button again after a 5 minutes interval if symptom recurs

Main symptom:		2nd Symptom:		OTHER:
Press ROUND button and record time		Record time only		Record symptom and time.

Appendix 3 – Bravo instructions and diary

Patient Instruction

The purpose of pH monitoring is to monitor the frequency and duration of gastro-oesophageal reflux during a normal day. It is important that you eat, drink, work and exercise as you normally would. Not keeping to your normal routine may mean that the test results do not reflect an accurate picture of your oesophageal pH exposure.

DO NOT take any acid suppressants (drugs such as Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Ranitidine, Metoclopramide, Domperidone or Gaviscon etc) during your study unless instructed to by your doctor.

Using the Patient Diary

Symptom Button	Symptom
	Heartburn
	Regurgitation
	Chest Pain

Record events (i.e. meals and sleep) in the patient diary using the time on the Receiver's display.

Using the Symptom Buttons

During the pH study symptoms (Heartburn, Regurgitation, Chest Pain) can be recorded in this diary or automatically recorded by pressing the appropriate symptom button.

Please only press the symptom button after 5 minute interval if the symptom recurs.

To confirm that the button has been pressed, a green indicator light remains lit for 3 seconds and a beep is heard if this feature is turned on.

Receiver out of range

If the Receiver is too far from the Bravo Capsule, a beep will be heard for 30 seconds and the display will flash C1 or C2. Move the Receiver to your breastbone until the beep stops and the C1 or C2 is no longer visible.

At the completion of your pH study, return the Bravo pH Receiver and your diary to the Oesophageal Laboratory, 4th Floor Bermondsey Wing, Guy's Hospital promptly. Any delay will cause inconvenience to other patients waiting for the Bravo test.

Instructions:

1. **Carry on with the next 48 hours as you would NORMALLY. Eg usual routine, normal meal times/portions etc**
2. **Chew your food well as this will help when swallowing**
3. **Use the clock on the recorder to record the time of your activities and write all times down in 24 hour clock format.**

Restrictions:

1. **Avoid acidic food and drink. Eg. PICKLES, TOMATO BASED FOOD, YOGHURT, FRUIT, SOFT DRINKS, FRUIT JUICE, ALCOHOL etc.**
2. **Always have milk with your tea or coffee to buffer the acidity. Otherwise drink milk, hot choc, horlicks or water only.**
3. **Make sure the receiver DOES NOT GET WET or drops into the toilet, so place the receiver in the dry place during showering or bathing**
4. **Use a maximum of two pillows when sleeping as we need you to lie as flat as possible**

If you have any problems or questions during the test, call 020 7188 4194 between 8am -4pm

BRAVO PATIENT DIARY

Start Time __:__ End Time __:__

Patient _____

Receiver _____

Day 1 ___ / ___ 20__

Start Time	End Time	Heartburn	Regurg.	Chest Pain	Meal	Sleep	Other	Comments

Day 2 ___ / ___ 20__

Day 3 ___ / ___ 20__

Day 4 ___ / ___ 20__

Appendix 4 - Inclusion/Exclusion criteria for patients recruited for Wireless pH Monitoring studies

Participants

Patients aged 18-65 with a history of predominantly typical reflux symptoms (e.g. heartburn, acid regurgitation) referred for Bravo-pH studies are eligible.

Inclusion Criteria

- Provision of written, fully informed consent to undergo mechanistic procedures: endoscopy, 4 day wireless pH monitoring by the Bravo system
- All subjects should be off acid suppression medication (e.g. PPI, H2RA) for at least 5 days prior to endoscopy

Exclusion Criteria

- Significant gastrointestinal symptoms or disease other than reflux
- Previous upper GI surgery or interventions such as oesophageal dilatations
- Predominant symptoms of motility disorders, e.g. dysphagia
- Presence of major oesophageal dysmotility on manometry, e.g. achalasia
- Significant co-morbidity requiring ongoing treatment or investigation
- Physical, neurological or psychiatric conditions preventing repeated visits to hospital or compliance with study procedures (e.g. physical impairment / reduced mobility)
- Pregnant at the time of enrolment
- No haematological abnormalities (no anticoagulants)

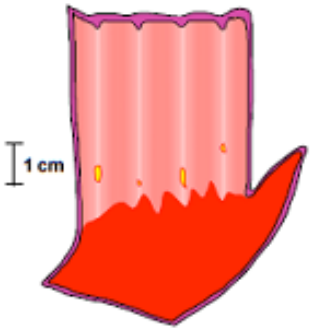
No medications influencing gastrointestinal function within 3 days of the study.

Appendix 5 – LA classification for Oesophagitis

LOS ANGELES CLASSIFICATION of Reflux Esophagitis

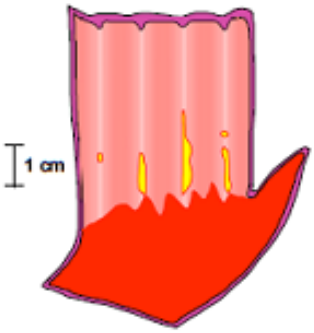
Developed by the International Working Group for the Classification of Reflux Oesophagitis (IWGCO)

LA Grade A



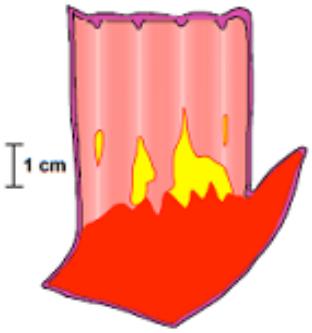
One (or more) mucosal break no longer than 5mm, that does not extend between the tops of two mucosal folds

LA Grade B



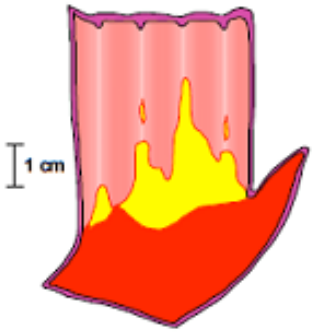
One (or more) mucosal break more than 5 mm long, that does not extend between the tops of two mucosal folds

LA Grade C



One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference

LA Grade D

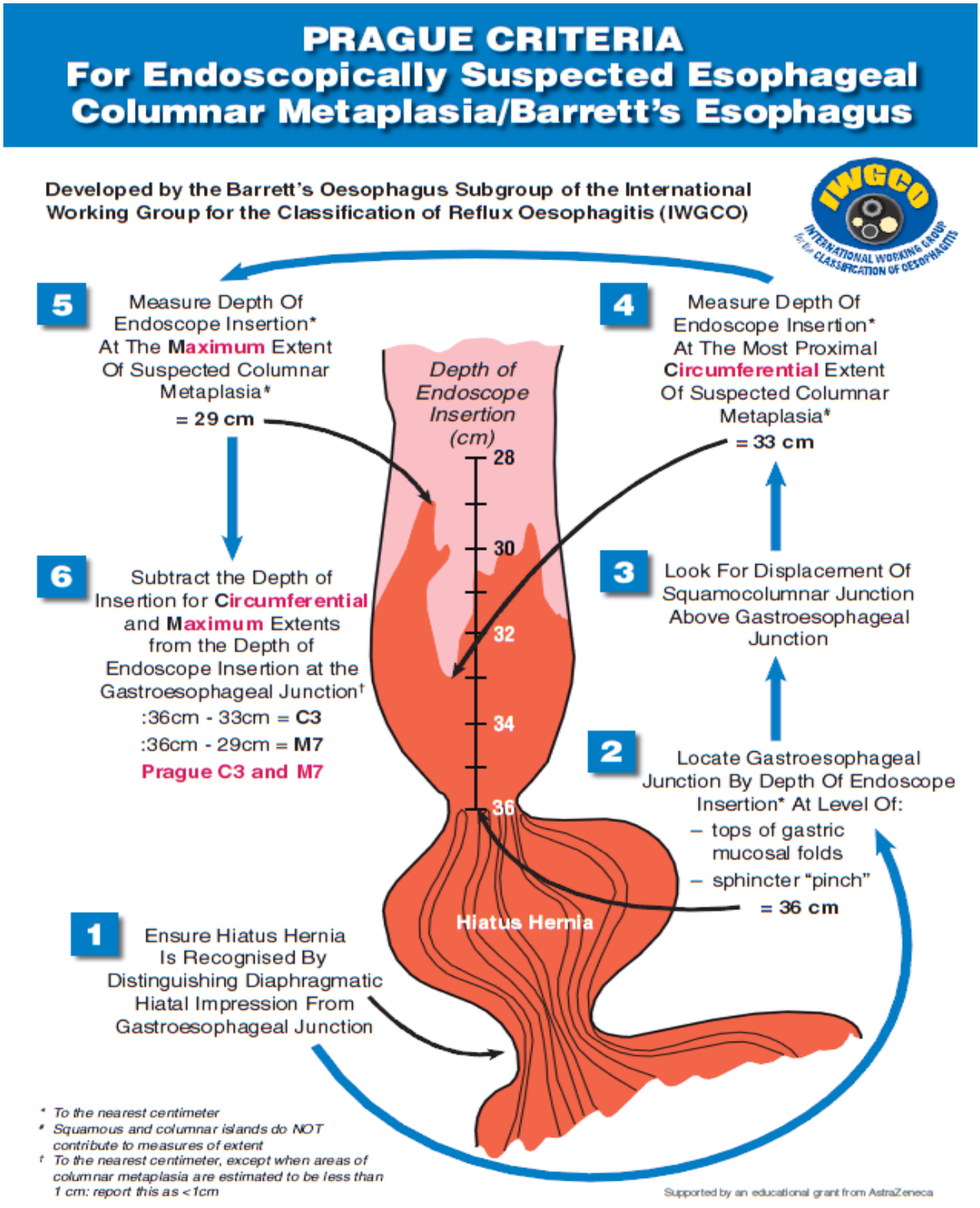


One (or more) mucosal break which involves at least 75% of the esophageal circumference

Lundell et al Gut 45:172-180 (1999)

Supported by an educational grant from AstraZeneca

Appendix 6 – Prague criteria for Barrett's



Appendix 7 – Ambulatory pH monitoring satisfaction questionnaire

Satisfaction Questionnaire for 24 hr pH catheter and Bravo

1. What was your overall experience of the system?

1 (very unhappy/intolerant)-2-3-4-5 (very satisfied)

2. Did you experience any chest pain immediately after placement of the device?

1 (very severe)-2-3-4-5 (none)

3. Did you experience any swallowing difficulty after the device was placed?

1 (very severe/unable to swallow)-2-3-4-5 (normal)

4. Did eating feel different?

1 (very unhappy/unable to eat)-2-3-4-5 (no difference)

5. Did you experience restriction in your daily activities? and how severe?

1 (very severe/unable to move)-2-3-4-5 (normal for me)

6. Did you go to work the day following the procedure?

yes no unemployed

7. Would you recommend this test to another person?

yes no

8. Did you experience throat discomfort?

1 (very severe)-2-3-4-5 (none)

9. Did you experience nasal discomfort?

1 (very severe)-2-3-4-5 (none)

Additional questions for Bravo Satisfaction Questionnaire

10. Do you think you were able to tell when the capsule fell off?

yes no

11. Would you prefer the Bravo system or the standard 24 hour catheter?

Bravo system Standard 24 hour catheter

12. Why was the standard 24 hour catheter test unsuccessful?

a. Failed insertion through the nose.
b. Unable to tolerate the catheter after it was placed.
c. Vomited pH catheter before the test was finished.

Appendix 8 - Inclusion/Exclusion criteria for healthy subjects and patients recruited for HRM

Study Population

Healthy volunteers will be recruited by local advertisement

Patients with oesophageal symptoms (reflux/dysphagia) will be recruited from lab

Inclusion criteria

1. male or female
2. at least 18 years of age
3. have given informed consent for the HRM procedure

Exclusion Criteria

For normal controls:

1. with symptoms or a history of oesophageal gastrointestinal disease
2. with regular intake of medication. Occasional analgesics (e.g. aspirin) is allowed
3. with any hematological abnormalities
4. with any evidence of infectious disease
5. who are pregnant or breast-feeding.
6. with evidence or history of drug or alcohol abuse within the past two years
7. with diabetes mellitus
8. with mental impairment limiting the ability to comply with study requirements
9. who are taking or planning to take other investigational drugs during the study
10. with use of medications influencing upper GI motility within one week of the study (i.e. calcium channel blockers, prokinetic drugs, macrolide antibiotics).
11. with use of PPIs and H2 blockers

For patients:

1. with no oesophageal symptoms (e.g. referred for studies prior to bariatric surgery)
2. with mental impairment limiting the ability to comply with study requirements
3. who are taking or planning to take other investigational drugs during the study
4. with use of medications influencing upper GI motility within one week of the study (i.e. calcium channel blockers, prokinetic drugs, macrolide antibiotics).

Interruption or discontinuation of treatment

Subjects who are unable to tolerate the HRM catheter or are unable to complete the test will be declared non-evaluable. The study is not a trial of treatment and will be analyzed on a per protocol basis. Thus, patients declared non-evaluable will be replaced to maintain numbers and sufficient power to detect the changes in oesophageal function.

Appendix 9 – Ethics approval + amendment for HRM healthy controls physiological study

St Thomas' Hospital Research Ethics Committee

South London REC Office 3
Ethics Committee Office
Governors' Hall Suite,
Ground Floor South Wing
St Thomas' Hospital
London
SE1 7EH

Tel: 0207 188 2257
Fax: 0207 188 2258

06 March 2008
Dr. Rami Sweis
SpR Gastroenterology
St Thomas' Hospital

Dear Dr. Sweis

Study title: **The effect of position on oesophageal peristalsis and LOS pressures: a high resolution manometry study**
REC reference: **07/Q0702/3**
Amendment number: **2**
Amendment date: **February 2008**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 26 February 2008.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents
The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	2 - Feb 2008	
Participant Consent Form	4 - Feb 2008	
Notice of Substantial Amendment (non-CTIMPs)		25 February 2008
Participant Information Sheet	4 - Feb 2008	

Membership of the Committee
The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/Q0702/3: Please quote this number on all correspondence

Yours sincerely

Stella Hirsch

Committee Co-ordinator

E-mail: stella.hirsch@gstt.sthames.nhs.uk

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to: *R & D Office, Guy's & St Thomas' NHS Foundation Trust*

St Thomas' Hospital Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 26 February 2008

Name	*Profession*	*Capacity*
Dr Adrian Hopper	Co Chair/Consultant Physician	Expert
Dr Adrian J Williams	Co Chair/Consultant Physician	Expert

Appendix 10 - Publications and talks arising from studies in this thesis

Original articles

- **Rami Sweis**, Angela Anggiansah, Terry Wong, Gareth Brady, Mark Fox Assessment of oesophageal dysfunction and symptoms during and after a standardized test meal in patients with reflux symptoms: a high-resolution manometry study. *Gut* (revision advised)
- **Rami Sweis**, Mark Fox, Angela Anggiansah, Terry Wong. Prolonged, wireless pH-studies have a high diagnostic yield in patients with reflux symptoms and negative 24-h catheter-based pH-studies. *Neurogastroenterol Motil* 2011;**23**(5)**:**419-26
- **Rami Sweis**, Angela Anggiansah, Terry Wong, Elad Kaufman, Sabina Obrecht, Mark Fox. Normative values and inter-observer agreement for liquid and solid bolus swallows in upright and supine positions as assessed by esophageal high-resolution manometry. *Neurogastroenterol Motil* 2011;**23**(6)**:**509-e198
- **Rami Sweis**, Mark Fox, Angela Anggiansah R, et al. Patient acceptance and clinical impact of Bravo monitoring in patients with previous failed catheter-based studies. *Aliment Pharmacol Ther* 2009;**29**(6)**:**669-76.

Invited reviews

- Mark Fox, **Rami Sweis**. Future Directions in Esophageal Motility and Function – New Technology and Methodology. *Neurogastroent Motil* 2012;24 Suppl 1:48-56.

Invited book chapters

- **Rami Sweis**. Oesophagus. In: Diet and Nutrition for Gastrointestinal Disease (Wiley Blackwell)
- **Rami Sweis,** Mark Fox**.** Free drinking and Solid Swallows using HRM In: Manual of High Resolution Esophageal manometry (Uni-Med Science) 2012
- **Rami Sweis**, Abraham Botha. Pathophysiology and investigation of gastro-oesophageal reflux disease. In: Griffin SM, Raimes SA, eds. Oesophagogastric Surgery. 4th ed: WB Saunders (Elsevier), 2009: 229-250.

Invited speaker (selected talks)

- Upper GI Day; Benign Oesophageal Disease conference; St Thomas' Hospital, London

  Therapeutic options in the treatment of dysphagia
- First Symposium on Gastro-esophageal Diseases: Present and Future of GERD; Fundacion Mutua Madrileña, Madrid
  - Wireless pH monitoring
- Advances in Clinical Oesophageal Investigation conference; Ascona, Switzerland
  - Wireless pH monitoring
  - Solid swallows and a test meal increase the clinical utility of High Resolution Manometry **- Prize for best oral presentation**
- European Society of Esophagology 2010; Controversies in Esophageal Disease; Frankfurt
  - Advances in High Resolution Manometry
- Royal London Hospital NGM meeting; Royal London Hospital, London
  - High Resolution Manometry; Physiological Challenge testing.
- Jordan Gastroenterology Society Congress; Amman
  - Advanced technology in the assessment of GORD and Dysmotility; Bravo wireless pH monitoring and High Resolution Manometry - **Keynote speaker**
- Gastro 2009 UEGW/WCOG; High Resolution Consensus Meeting - The Next Steps: Z-HRM, test meals and other advances
  - Inclusion of solid swallows and a test meal increase the clinical utility of High Resolution Manometry in patients with dysphagia
  - Solid swallows and a test meal increase the clinical utility of High Resolution Manometry in patients presenting with reflux symptoms
- St. George's Gastroenterology Day; St George's Hospital, London
  - Advances in Investigation of Oesophageal Dysmotility and Reflux Disease
- British Society of Gastroenterology**;** Glasgow - **Keynote speaker**
  - Investigation and treatment of the patient that fails to respond to PPIs.
- European Society of Neurogastroenterology and Motility Meeting; Lucerne
  - High Resolution Manometry with large volume multiple repeated swallows aids detection of oesophageal pathology

Selected oral abstracts

- **Rami Sweis**, Angela Anggiansah, Roy Anggiansah, Jayne Fong, Terry Wong, Mark R. Fox. Inclusion of solid swallows and a test meal increase the diagnostic yield of High Resolution Manometry (HRM) in patients with dysphagia. *Gastroenterology* 2011; 140 (Supplement 1)(5): S-77
- **Rami Sweis**, Angela Anggiansah, Terry Wong, Mark R. Fox. Solid swallows and a test meal increase the clinical utility of High Resolution Manometry in patients presenting with reflux symptoms - Joint Regional BSG society meeting (2010)
  1st place prize
- **Rami Sweis**, Angela Anggiansah, Terry Wong, Mark R. Fox. The effect of 'physiologic challenge' on coordination between proximal and distal oesophageal contractions in healthy volunteers. King's College London Nutritional Society Symposium. (2010)
- **Rami Sweis**, Angela Anggiansah, Mark R. Fox, Terry Wong, 96 hour bravo increases yield in patients with negative 24 hour oesophageal catheter pH tests results. *Gut* 2009;58:Suppl 1 A1-A156.

Selected posters

- **Rami Sweis**, Angela Anggiansah, Terry Wong, Mark R. Fox. Normal Values for Esophageal Motility and Function During Multiple Swallows of Low vs. High Consistency Liquid. *Gastroenterology* 2011; 140 (Supplement 1)(5): S-869-S-870
- **Rami Sweis**, Angela Anggiansah, Roy Anggiansah, Jayne Fong, Terry Wong, Mark R. Fox. Inclusion of solid swallows and a test meal increase the diagnostic yield of High Resolution Manometry (HRM) in patients with reflux symptoms. *Gastroenterology* 2011; 140 (Supplement 1)(5): S-231
- **Rami Sweis,** Angela Anggiansah, Terry Wong, Mark Fox. The effect of bolus consistency and position change on the coordination of peristaltic contractions in healthy volunteers. *Gut* 2011;60:Suppl 1 A186 – **Distinction**
- **Rami Sweis,** Angela Anggiansah, Terry Wong, Mark Fox. High resolution manometry during a standardised test meal and free drinking. *Gut* 2011;60:Suppl 1 A185

- **Rami Sweis**, Elad Kaufman, Sabina Obrecht, et al. Inter-observer agreement of water and solid swallows in high resolution manometry. *Gut* 2011;60:Suppl 1 A184-A185
- **Rami Sweis,** Angela Anggiansah, Terry Wong, Mark Fox. The effect of 'physiologic challenge' on coordination between proximal and distal esophageal contractions in healthy volunteers. *Gastroenterology* 2010; 138 (Supplement 1)(5): S-600. (T1890)
- **Rami Sweis,** Angela Anggiansah, Terry Wong, Mark Fox. Effects of bolus consistency and body position on oesophageal function assessed by High Resolution Manometry. *Gastro* 2009 UEGW/WCOG P1624.
- **Rami Sweis**, Terry Wong, Angela Anggiansah, Mark Fox. Normal values for HRM assessment of liquid, solid and multiple repeated swallows in the upright and supine positions. *Gut* 2009;58(Suppl I):A1–A156
- **Rami Sweis,** Terry Wong, Angela Anggiansah, Mark Fox. High resolution manometry with large volume Multiple Rapid Swallows aids the detection of esophageal pathology. *Gastroenterology* 2009; 136, Supplement 1(5):A-286. (S1892) - **Distinction**